

Attorney Docket No.: 6692.204-US
Applicants: Lau et al.
Title: Novel GLP-Derivatives
Filed: March 17, 2006
Express Mail Label No.: EV 732209960 US

IN THE CLAIMS:

Claims 1-72 (Cancelled)

Claim 73 (New) A compound which comprises a therapeutic polypeptide linked to an albumin binding residue via a hydrophilic spacer.

Claim 74 (New) A compound which comprises a therapeutic polypeptide linked to an albumin binding residue via a hydrophilic spacer $-(CH_2)_lD[(CH_2)_nE]_m(CH_2)_pQ_q-$, wherein

l, m and n independently are 1-20 and p is 0-10,

Q is $-Z-(CH_2)_lD[(CH_2)_nG]_m(CH_2)_p-$,

q is an integer in the range from 0 to 5,

each D, E, and G independently are selected from $-O-$, $-NR^3-$, $-N(COR^4)-$, $-PR^5(O)-$, and $-P(OR^6)(O)-$, wherein R^3 , R^4 , R^5 , and R^6 independently represent hydrogen or C_{1-6} -alkyl,

Z is selected from $-C(O)NH-$, $-C(O)NHCH_2-$, $-OC(O)NH-$, $-C(O)NHCH_2CH_2-$, $-C(O)CH_2-$,

$-C(O)CH=CH-$, $-(CH_2)_s-$, $-C(O)-$, $-C(O)O-$ or $-NHC(O)-$, wherein s is 0 or 1

or a pharmaceutically acceptable salt or prodrug thereof.

Claim 75 (New) A compound according to claim 74, which has formula (I) :



wherein

A is an albumin binding residue,

B is a hydrophilic spacer being $-(CH_2)_lD[(CH_2)_nE]_m(CH_2)_pQ_q-$, wherein

l, m and n independently are 1-20 and p is 0-10,

Q is $-Z-(CH_2)_lD[(CH_2)_nG]_m(CH_2)_p-$,

q is an integer in the range from 0 to 5,

each D, E, and G independently are selected from $-O-$, $-NR^3-$, $-N(COR^4)-$, $-PR^5(O)-$, and $-P(OR^6)(O)-$, wherein R^3 , R^4 , R^5 , and R^6 independently represent hydrogen or C_{1-6} -alkyl,

Z is selected from $-C(O)NH-$, $-C(O)NHCH_2-$, $-OC(O)NH-$, $-C(O)NHCH_2CH_2-$, $-C(O)CH_2-$,

$-C(O)CH=CH-$, $-(CH_2)_s-$, $-C(O)-$, $-C(O)O-$ or $-NHC(O)-$, wherein s is 0 or 1,

Y is a chemical group linking B and the therapeutic agent, and

W is a chemical group linking A and B.

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Claim 76 (New) A compound according to claim 74, which has formula (II)



wherein

A and A' are albumin binding residues,

B and B' are hydrophilic spacers independently selected from $-(CH_2)_lD[(CH_2)_nE]_m(CH_2)_pQ_q-$,

wherein

l, m and n independently are 1-20 and p is 0-10,

Q is $-Z-(CH_2)_lD[(CH_2)_nG]_m(CH_2)_p-$,

q is an integer in the range from 0 to 5,

each D, E, and G independently are selected from $-O-$, $-NR^3-$, $-N(COR^4)-$, $-PR^5(O)-$, and $-P(OR^6)(O)-$, wherein R^3 , R^4 , R^5 , and R^6 independently represent hydrogen or C_{1-6} -alkyl,

Z is selected from $-C(O)NH-$, $-C(O)NHCH_2-$, $-OC(O)NH-$, $-C(O)NHCH_2CH_2-$, $-C(O)CH_2-$,

$-C(O)CH=CH-$, $-(CH_2)_s-$, $-C(O)-$, $-C(O)O-$ or $-NHC(O)-$, wherein s is 0 or 1,

Y is a chemical group linking B and the therapeutic agent, and

Y' is a chemical group linking B' and the therapeutic agent, and

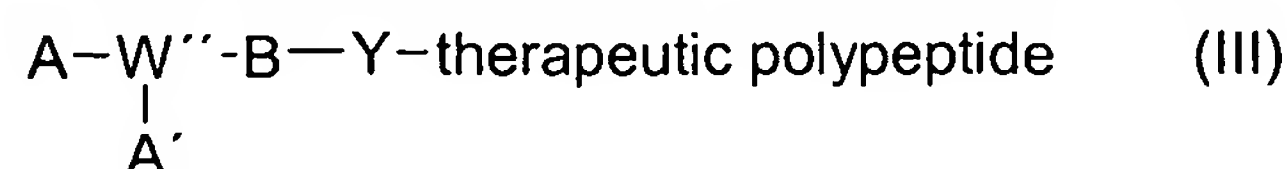
W is a chemical group linking A and B, and

W' is a chemical group linking A' and B'.

Claim 77 (New) A compound according to claim 76, wherein Y' is selected from the group consisting of $-C(O)NH-$, $-NHC(O)-$, $-C(O)NHCH_2-$, $-CH_2NHC(O)-$, $-OC(O)NH-$, $-NHC(O)O-$, $-C(O)NHCH_2-$, $-CH_2NHC(O)-$, $-C(O)CH_2-$, $-CH_2C(O)-$, $-C(O)CH=CH-$, $-CH=CHC(O)-$, $-(CH_2)_s-$, $-C(O)-$, $-C(O)O-$, $-OC(O)-$, $-NHC(O)-$ and $-C(O)NH-$, wherein s is 0 or 1.

Claim 78 (New) A compound according to claim 76, wherein W' is selected from the group consisting of $-C(O)NH-$, $-NHC(O)-$, $-C(O)NHCH_2-$, $-CH_2NHC(O)-$, $-OC(O)NH-$, $-NHC(O)O-$, $-C(O)CH_2-$, $-CH_2C(O)-$, $-C(O)CH=CH-$, $-CH=CHC(O)-$, $-(CH_2)_s-$, $-C(O)-$, $-C(O)O-$, $-OC(O)-$, $-NHC(O)-$ and $-C(O)NH-$, wherein s is 0 or 1.

Claim 79 (New) A compound according to claim 74, which has formula (III)



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wherein

A and A' are albumin binding residues,

B is a hydrophilic spacer selected from $-(CH_2)_lD[(CH_2)_nE]_m(CH_2)_p-Q_q-$ wherein

l, m and n independently are 1-20 and p is 0-10,

Q is $-Z-(CH_2)_lD[(CH_2)_nG]_m(CH_2)_p-$,

q is an integer in the range from 0 to 5,

each D, E, and G are independently selected from $-O-$, $-NR^3-$, $-N(COR^4)-$, $-PR^5(O)-$, and $-P(OR^6)(O)-$, wherein R^3 , R^4 , R^5 , and R^6 independently represent hydrogen or C_{1-6} -alkyl,

Z is selected from $-C(O)NH-$, $-C(O)NHCH_2-$, $-OC(O)NH-$, $-C(O)NHCH_2CH_2-$, $-C(O)CH_2-$, $-C(O)CH=CH-$, $-(CH_2)_s-$, $-C(O)-$, $-C(O)O-$ or $-NHC(O)-$, wherein s is 0 or 1,

Y is a chemical group linking B and the therapeutic agent, and

W'' is a chemical group linking B with A and A'.

Claim 80 (New) A compound according to claim 79, wherein W'' is selected from the group consisting of

$-C(O)NHCH-$, $-C(O)CH-$, $-(CH_2)_sCH-$, and $-NHC(O)C(NHC(O)CH_2O(CH_2)_2O(CH_2)_2NH-$,
 | | |
 , wherein s is 0, 1 or 2.

Claim 81 (New) A compound according to claim 75, wherein Y is selected from the group consisting of $-C(O)NH-$, $-NHC(O)-$, $-C(O)NHCH_2-$, $-CH_2NHC(O)-$, $-OC(O)NH-$, $-NHC(O)O-$, $-C(O)NHCH_2-$, $-CH_2NHC(O)-$, $-C(O)CH_2-$, $-CH_2C(O)-$, $-C(O)CH=CH-$, $-CH=CHC(O)-$, $-(CH_2)_s-$, $-C(O)-$, $-C(O)O-$, $-OC(O)-$, $-NHC(O)-$ and $-C(O)NH-$, wherein s is 0 or 1.

Claim 82 (New) A compound according to claim 75, wherein W is selected from the group consisting of $-C(O)NH-$, $-NHC(O)-$, $-C(O)NHCH_2-$, $-CH_2NHC(O)-$, $-OC(O)NH-$, $-NHC(O)O-$, $-C(O)CH_2-$, $-CH_2C(O)-$, $-C(O)CH=CH-$, $-CH=CHC(O)-$, $-(CH_2)_s-$, $-C(O)-$, $-C(O)O-$, $-OC(O)-$, $-NHC(O)-$ and $-C(O)NH-$, wherein s is 0 or 1.

Claim 83 (New) A compound according to claim 74, wherein l is 1 or 2, n and m are independently 1-10 and p is 0-10.

Claim 84 (New) A compound according to claim 74, wherein D is $-O-$.

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Claim 85 (New) A compound according to claim 74, wherein E is $-O-$.

Claim 86 (New) A compound according to claim 74, wherein the hydrophilic spacer is $-CH_2O[(CH_2)_2O]_m(CH_2)_pQ_q-$, where m is 1-10, p is 1-3, and Q is $-Z-CH_2O[(CH_2)_2O]_m(CH_2)_p-$.

Claim 87 (New) A compound according to claim 74, wherein q is 0 or 1.

Claim 88 (New) A compound according to claim 74, wherein q is 1.

Claim 89 (New) A compound according to claim 74, wherein G is $-O-$.

Claim 90 (New) A compound according to claim 74, wherein Z is selected from the group consisting of $-C(O)NH-$, $-C(O)NHCH_2-$, and $-OC(O)NH-$.

Claim 91 (New) A compound according to claim 74, wherein q is 0.

Claim 92 (New) A compound according to claim 74, wherein l is 2.

Claim 93 (New) A compound according to claim 74, wherein n is 2.

Claim 94 (New) A compound according to claim 74, wherein the hydrophilic spacer B is $-[CH_2CH_2O]_{m+1}(CH_2)_pQ_q-$.

Claim 95 (New) A compound according to claim 74, wherein the hydrophilic spacer B is $-(CH_2)_l-O-[(CH_2)_n-O]_m-(CH_2)_p-[C(O)NH-(CH_2)_l-O-[(CH_2)_n-O]_m-(CH_2)_p]_q-$, where l, m, n, and p independently are 1-5, and q is 0-5.

Claim 96 (New) A compound according to claim 75, wherein $-W-B-Y-$ is selected from the group consisting of

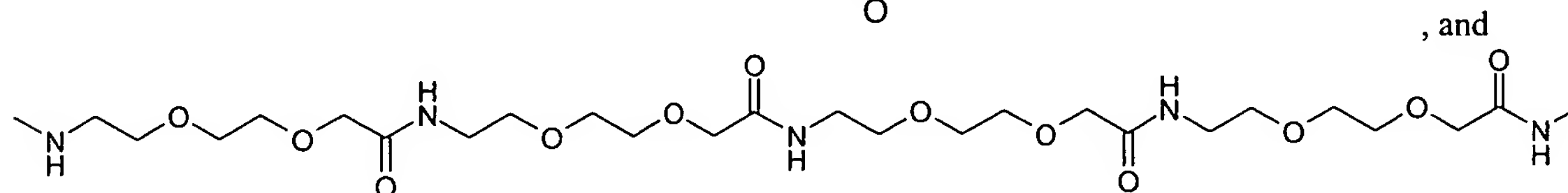
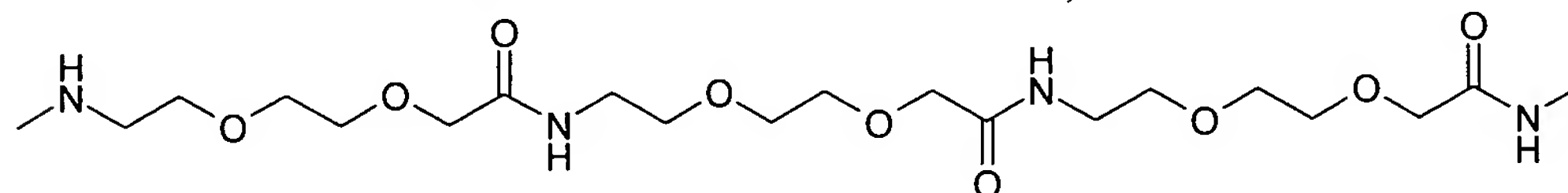
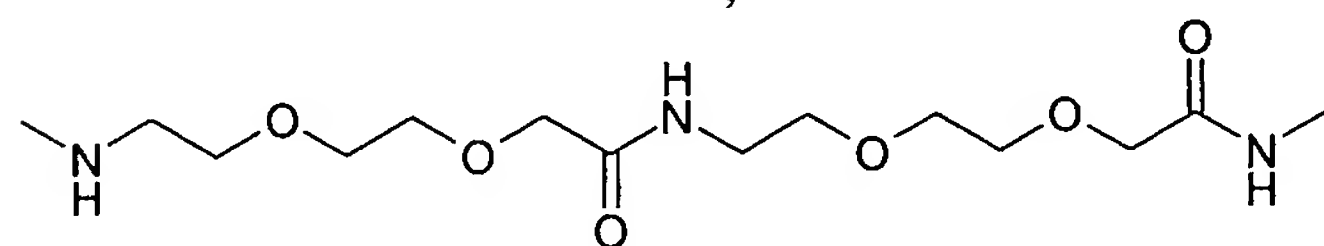
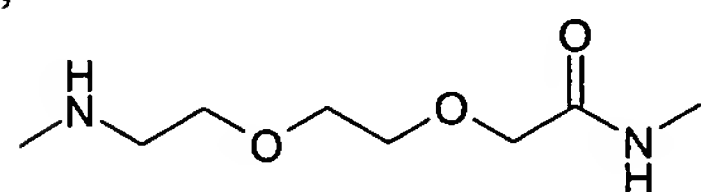
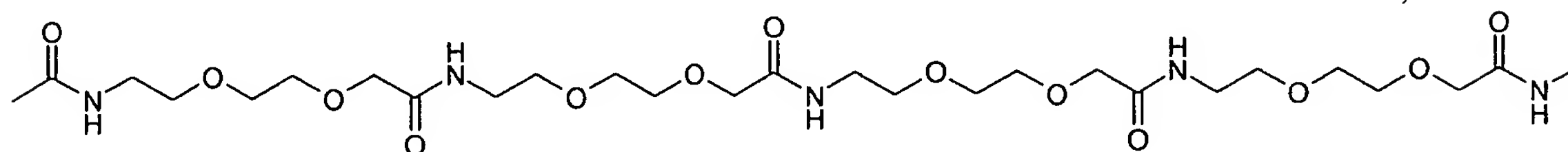
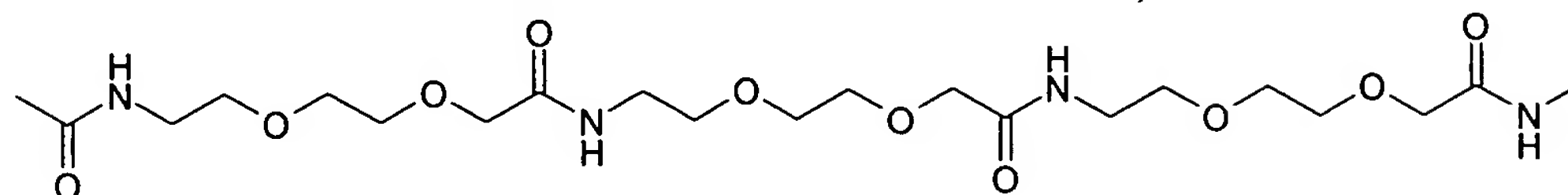
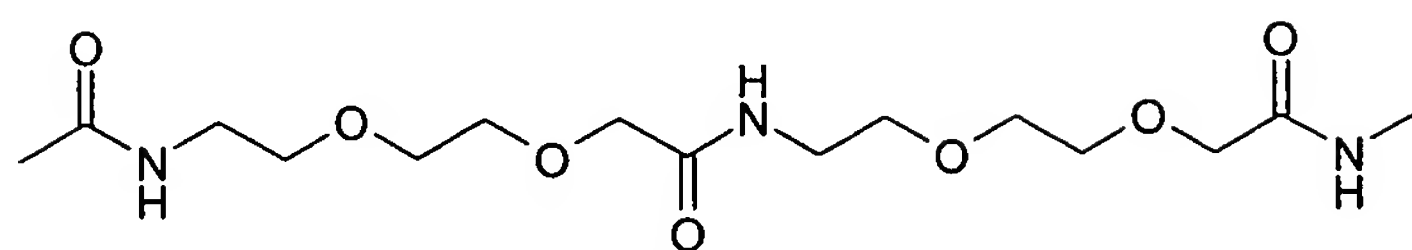
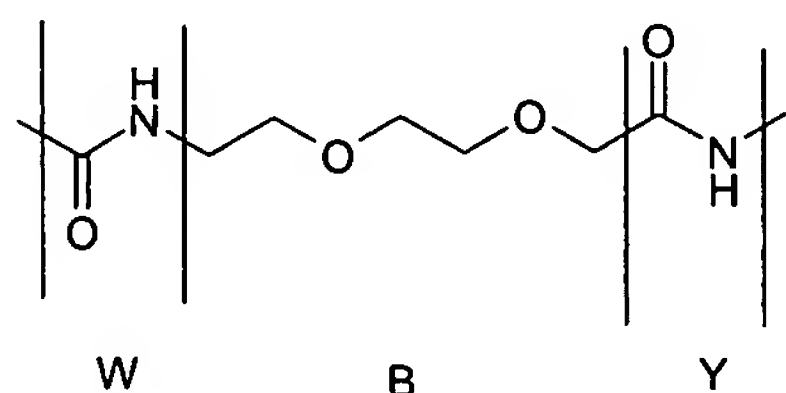
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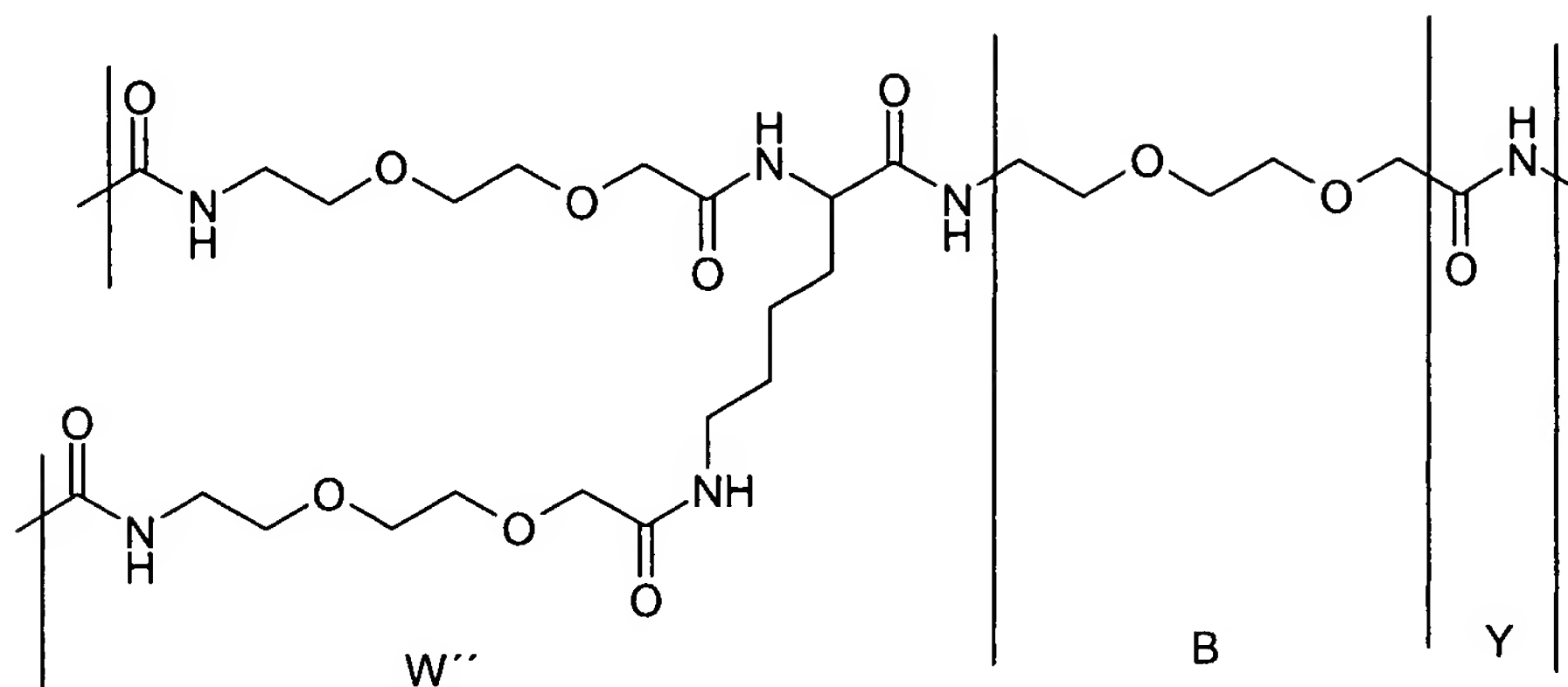
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Claim 97 (New) A compound according to claim 79, wherein >W''-B-Y- is

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Claim 98 (New) A compound according to claim 73, wherein the molar weight of said hydrophilic spacer is in the range from 80D to 1000D or in the range from 80D to 300D.

Claim 99 (New) A compound according to claim 73, wherein said albumin binding residue is a lipophilic residue.

Claim 100 (New) A compound according to claim 73, wherein said albumin binding residue binds non-covalently to albumin.

Claim 101 (New) A compound according to claim 73, wherein said albumin binding residue is negatively charged at physiological pH.

Claim 102 (New) A compound according to claim 73, wherein said albumin binding residue has a binding affinity towards human serum albumin that is below about 10 μ M.

Claim 103 (New) A compound according to claim 73, wherein said albumin binding residue is selected from a straight chain alkyl group, a branched alkyl group, a group which has an ω -carboxylic acid group, a partially or completely hydrogenated cyclopentanophenanthrene skeleton.

Claim 104 (New) A compound according to claim 73, wherein said albumin binding residue is a cibacronyl residue.

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Claim 105 (New) A compound according to claim 73, wherein said albumin binding residue has from 6 to 40 carbon atoms.

Claim 106 (New) A compound according to claim 73, wherein said albumin binding residue is a peptide.

Claim 107 (New) A compound according to claim 73, wherein the albumin binding residue via spacer and linkers is attached to said therapeutic polypeptide via the ϵ -amino group of a lysine residue.

Claim 108 (New) A compound according to claim 73, wherein the albumin binding residue via spacer and linkers is attached to said therapeutic polypeptide via a linker to an amino acid residue selected from cysteine, glutamate and aspartate.

Claim 109 (New) A compound according to claim 73, wherein said therapeutic polypeptide is a glucagon-like peptide 1 (GLP-1) peptide.

Claim 110 (New) A compound according to claim 109, wherein said polypeptide is a GLP-1 peptide comprising the amino acid sequence of the formula (IV):

Xaa₇-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Xaa₁₆-Ser-Xaa₁₈-Xaa₁₉-Xaa₂₀-Glu-Xaa₂₂-Xaa₂₃-Ala-Xaa₂₅-
Xaa₂₆-Xaa₂₇-Phe-Ile-Xaa₃₀-Trp-Leu-Xaa₃₃-Xaa₃₄-Xaa₃₅-Xaa₃₆-Xaa₃₇-Xaa₃₈-Xaa₃₉-Xaa₄₀-Xaa₄₁-Xaa₄₂-
Xaa₄₃-Xaa₄₄-Xaa₄₅-Xaa₄₆

Formula (IV) (SEQ ID No: 2)

wherein

Xaa₇ is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, β -hydroxy-histidine, homohistidine, N ^{α} -acetyl-histidine, α -fluoromethyl-histidine, α -methyl-histidine, 3-pyridylalanine, 2-pyridylalanine or 4-pyridylalanine;

Xaa₈ is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa₁₆ is Val or Leu;

Xaa₁₈ is Ser, Lys or Arg;

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Xaa₁₉ is Tyr or Gln;

Xaa₂₀ is Leu or Met;

Xaa₂₂ is Gly, Glu or Aib;

Xaa₂₃ is Gln, Glu, Lys or Arg;

Xaa₂₅ is Ala or Val;

Xaa₂₆ is Lys, Glu or Arg;

Xaa₂₇ is Glu or Leu;

Xaa₃₀ is Ala, Glu or Arg;

Xaa₃₃ is Val or Lys;

Xaa₃₄ is Lys, Glu, Asn or Arg;

Xaa₃₅ is Gly or Aib;

Xaa₃₆ is Arg, Gly or Lys;

Xaa₃₇ is Gly, Ala, Glu, Pro, Lys, amide or is absent;

Xaa₃₈ is Lys, Ser, amide or is absent.

Xaa₃₉ is Ser, Lys, amide or is absent;

Xaa₄₀ is Gly, amide or is absent;

Xaa₄₁ is Ala, amide or is absent;

Xaa₄₂ is Pro, amide or is absent;

Xaa₄₃ is Pro, amide or is absent;

Xaa₄₄ is Pro, amide or is absent;

Xaa₄₅ is Ser, amide or is absent;

Xaa₄₆ is amide or is absent ;

provided that if Xaa₃₈, Xaa₃₉, Xaa₄₀, Xaa₄₁, Xaa₄₂, Xaa₄₃, Xaa₄₄, Xaa₄₅ or Xaa₄₆ is absent then each amino acid residue downstream is also absent.

Claim 111 (New) . A compound according to claim 110, wherein said polypeptide is a GLP-1 peptide comprising the amino acid sequence of formula (V):

Xaa₇-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Xaa₁₈-Tyr-Leu-Glu-Xaa₂₂-Xaa₂₃-Ala-Ala-Xaa₂₆-
Glu-Phe-Ile-Xaa₃₀-Trp-Leu-Val-Xaa₃₄-Xaa₃₅-Xaa₃₆-Xaa₃₇-Xaa₃₈

Formula (V) (SEQ ID No: 3)

wherein

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Xaa₇ is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, β -hydroxy-histidine, homohistidine, N ^{α} -acetyl-histidine, α -fluoromethyl-histidine, α -methyl-histidine, 3-pyridylalanine, 2-pyridylalanine or 4-pyridylalanine;

Xaa₈ is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa₁₈ is Ser, Lys or Arg;

Xaa₂₂ is Gly, Glu or Aib;

Xaa₂₃ is Gln, Glu, Lys or Arg;

Xaa₂₆ is Lys, Glu or Arg;

Xaa₃₀ is Ala, Glu or Arg;

Xaa₃₄ is Lys, Glu or Arg;

Xaa₃₅ is Gly or Aib;

Xaa₃₆ is Arg or Lys;

Xaa₃₇ is Gly, Ala, Glu or Lys;

Xaa₃₈ is Lys, amide or is absent.

Claim 112 (New) A compound according to claim 109, wherein said GLP-1 peptide is selected from GLP-1(7-35), GLP-1(7-36), GLP-1(7-36)-amide, GLP-1(7-37), GLP-1(7-38), GLP-1(7-39), GLP-1(7-40), GLP-1(7-41) or an analogue thereof.

Claim 113 (New) A compound according to claim 109, wherein said GLP-1 peptide comprises no more than ten amino acid residues which have been exchanged, added or deleted as compared to GLP-1(7-37) (SEQ ID No. 1).

Claim 114 (New) A compound according to claim 113, wherein said GLP-1 peptide comprises no more than six amino acid residues which have been exchanged, added or deleted as compared to GLP-1(7-37) (SEQ ID No. 1).

Claim 115 (New) A compound according to claim 113, wherein said GLP-1 peptide comprises no more than 4 amino acid residues which are not encoded by the genetic code.

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Claim 116 (New) A compound according to claim 109, wherein said GLP-1 peptide is a DPPIV protected GLP-1 peptide.

Claim 117 (New) A compound according to claim 109, wherein said compound is DPPIV stabilised.

Claim 118 (New) A compound according to claim 109, wherein said GLP-1 peptide comprises an Aib residue in position 8.

Claim 119 (New) A compound according to claim 109, wherein the amino acid residue in position 7 of said GLP-1 peptide is selected from the group consisting of D-histidine, desamino-histidine, 2-amino-histidine, β -hydroxy-histidine, homohistidine, N ^{α} -acetyl-histidine, α -fluoromethyl-histidine, α -methyl-histidine, 3-pyridylalanine, 2-pyridylalanine and 4-pyridylalanine.

Claim 120 (New) A compound according to claim 109, wherein said GLP-1 peptide is selected from the group consisting of Arg³⁴GLP-1(7-37), Lys³⁸Arg^{26,34}GLP-1(7-38), Lys³⁸Arg^{26,34}GLP-1(7-38)-OH, Lys³⁶Arg^{26,34}GLP-1(7-36), Aib^{8,22,35}GLP-1(7-37), Aib^{8,35}GLP-1(7-37), Aib^{8,22}GLP-1(7-37), Aib^{8,22,35}Arg^{26,34}Lys³⁸GLP-1(7-38), Aib^{8,35}Arg^{26,34}Lys³⁸GLP-1(7-38), Aib^{8,22}Arg^{26,34}Lys³⁸GLP-1(7-38), Aib^{8,22,35}Arg^{26,34}Lys³⁸GLP-1(7-38), Aib^{8,35}Arg^{26,34}Lys³⁸GLP-1(7-38), Aib^{8,22,35}Arg²⁶Lys³⁸GLP-1(7-38), Aib^{8,35}Arg²⁶Lys³⁸GLP-1(7-38), Aib^{8,22}Arg²⁶Lys³⁸GLP-1(7-38), Aib^{8,22,35}Arg³⁴Lys³⁸GLP-1(7-38), Aib^{8,35}Arg³⁴Lys³⁸GLP-1(7-38), Aib^{8,22}Arg³⁴Lys³⁸GLP-1(7-38), Aib^{8,22,35}Ala³⁷Lys³⁸GLP-1(7-38), Aib^{8,35}Ala³⁷Lys³⁸GLP-1(7-38), Aib^{8,22}Ala³⁷Lys³⁸GLP-1(7-38), Aib^{8,22,35}Lys³⁷GLP-1(7-37), Aib^{8,35}Lys³⁷GLP-1(7-37) and Aib^{8,22}Lys³⁷GLP-1(7-38).

Claim 121 (New) A compound according to claim 109, wherein said GLP-1 peptide is attached to said hydrophilic spacer via the amino acid residue in position 23, 26, 34, 36 or 38 relative to the amino acid sequence SEQ ID No:1.

Claim 122 (New) A compound according to claim 109, wherein said GLP-1 peptide is exendin-4.

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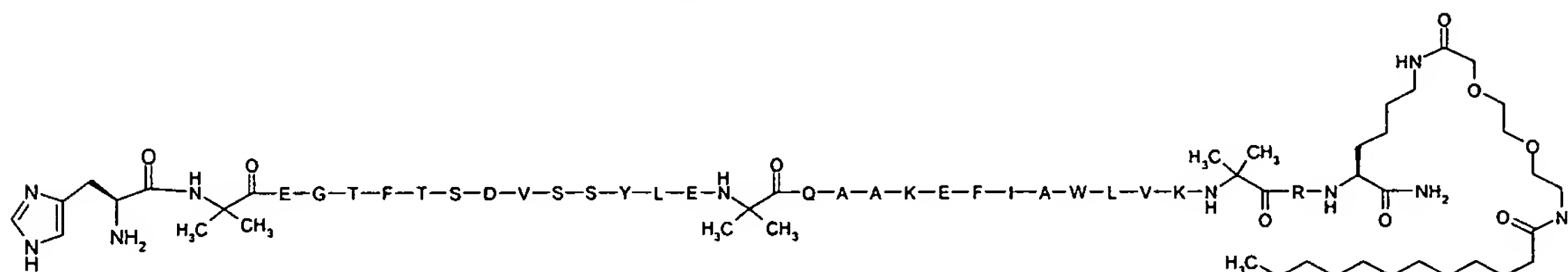
Claim 123 (New) A compound according to claim 109, wherein said GLP-1 peptide is HEGTFTSDLSKQMEEAVRLFIEWLKNGGPSSGAPPSKKKKKK-amide.

Claim 124 (New) A compound according to claim 109, wherein one albumin binding residue via said hydrophilic spacer is attached to the C-terminal amino acid residue of said GLP-1 peptide.

Claim 125 (New) A compound according to claim 124, wherein a second albumin binding residue is attached to an amino acid residue which is not the C-terminal amino acid residue.

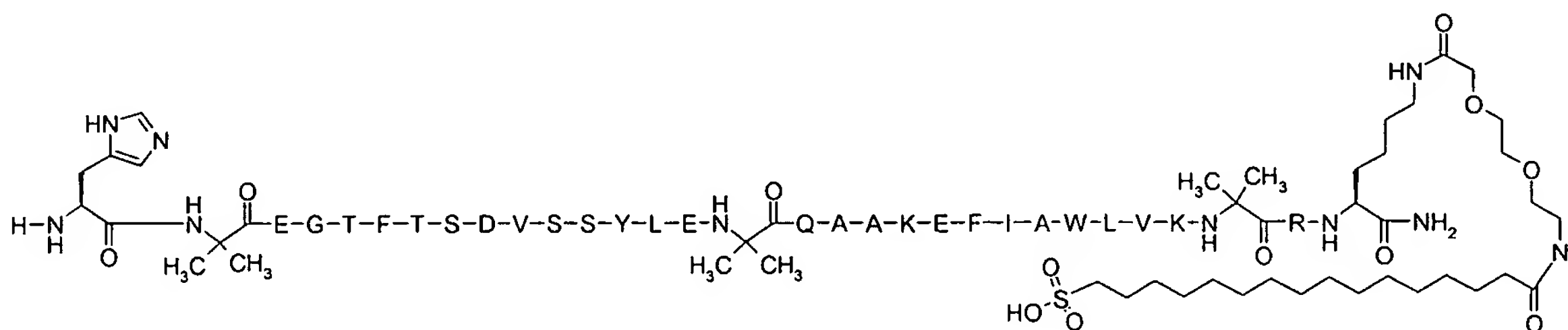
Claim 126 (New) A compound according to claim 73, wherein said compound is selected from the group consisting of

$N^{\square\square\square}$ -(2-(2-(2-(dodecylamino)ethoxy)ethoxy)acetyl)-[Aib^{8,22,35}Lys³⁷]GLP-1(7-37)amide



,

$N^{\square\square\square}$ -(2-(2-(2-(17-sulphohexadecanoylamino)ethoxy)ethoxy)acetyl)-[Aib^{8,22,35},Lys³⁷] GLP-1 (7-37)amide



,

$N^{\square\square\square}$ -{2-[2-(2-(15-carboxypentadecanoylamino)ethoxy)ethoxy]acetyl}-[Aib^{8,22,35},Lys³⁷] GLP-1(7-37)amide

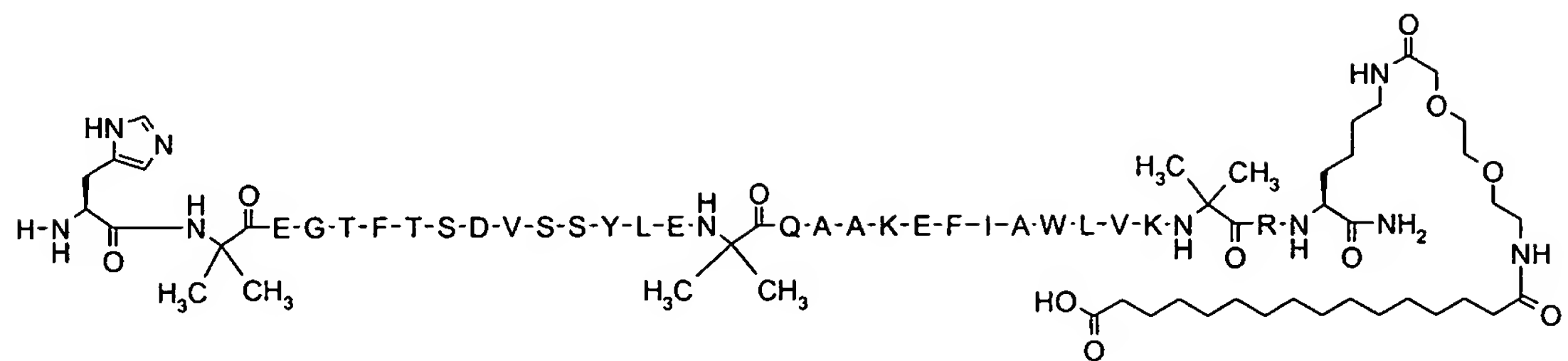
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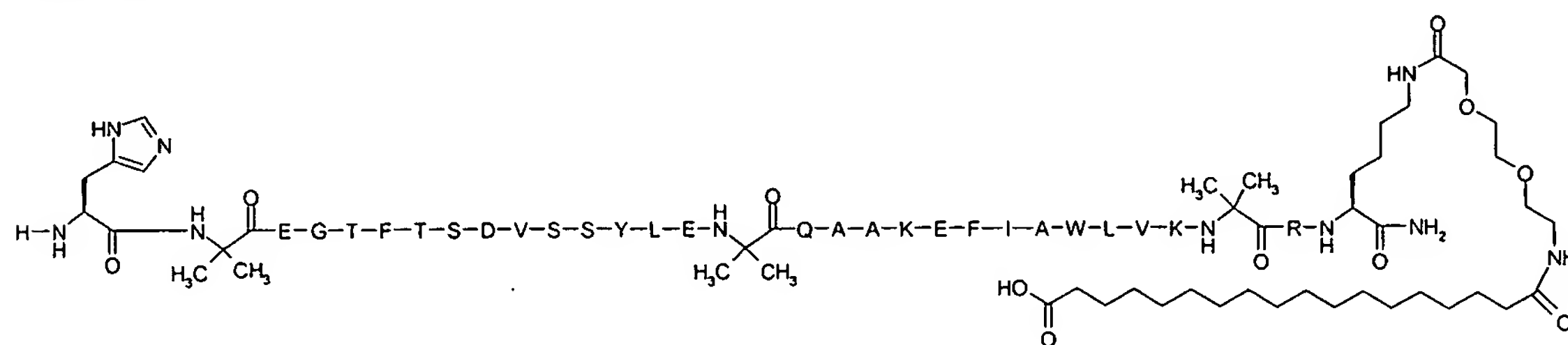
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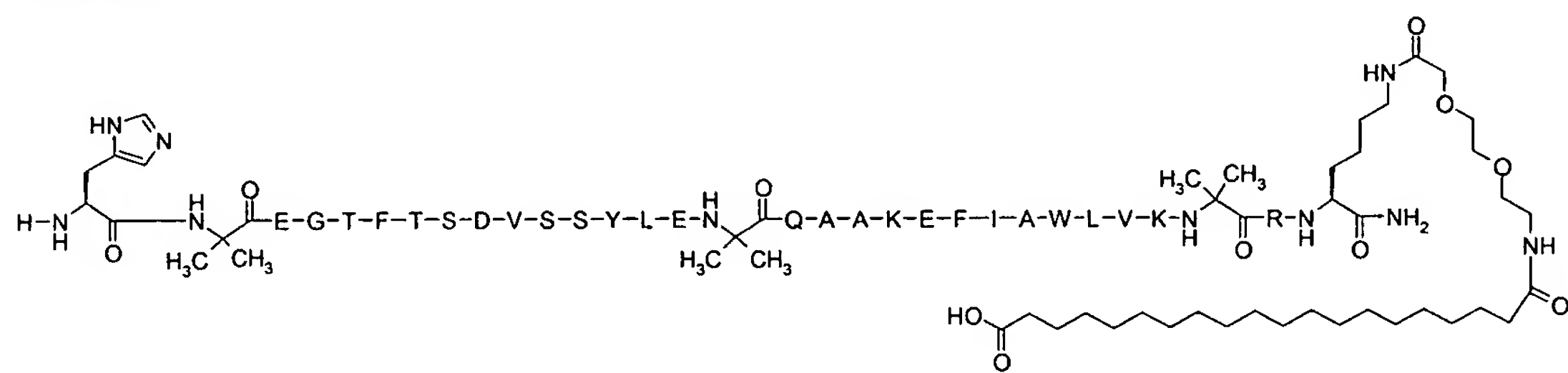
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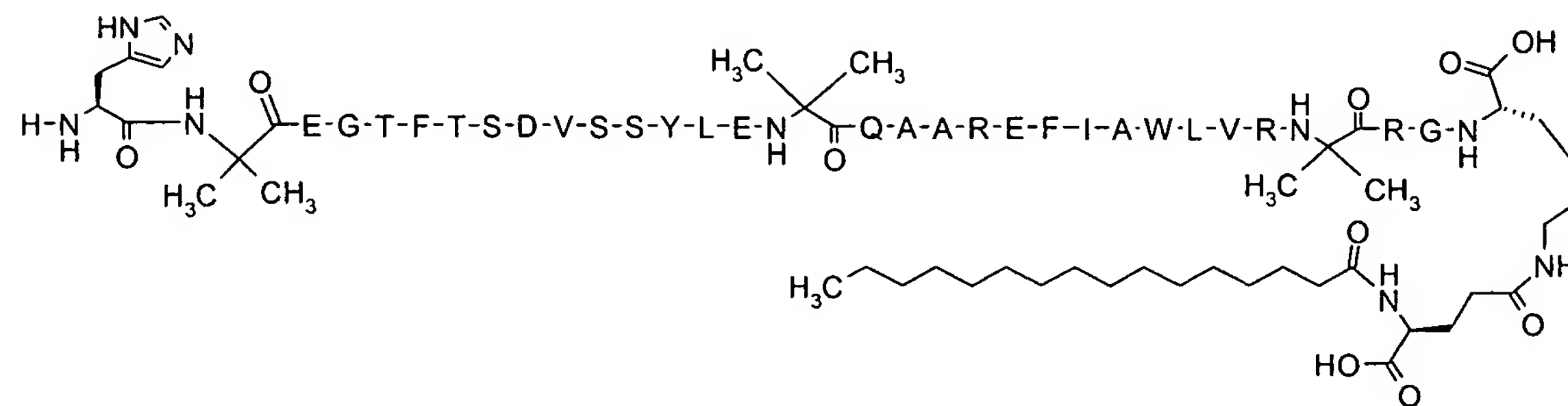
N^{□□□}-(2-(2-(2-(17-carboxyheptadecanoylamino)ethoxy)ethoxy)acetyl)[Aib^{8,22,35},Lys³⁷]GLP-1(7-37)amide



N^{□□□}-(2-(2-(2-(19-carboxynonadecanoylamino)ethoxy)ethoxy)acetyl)[Aib^{8,22,35},Lys³⁷]GLP-1(7-37)amide

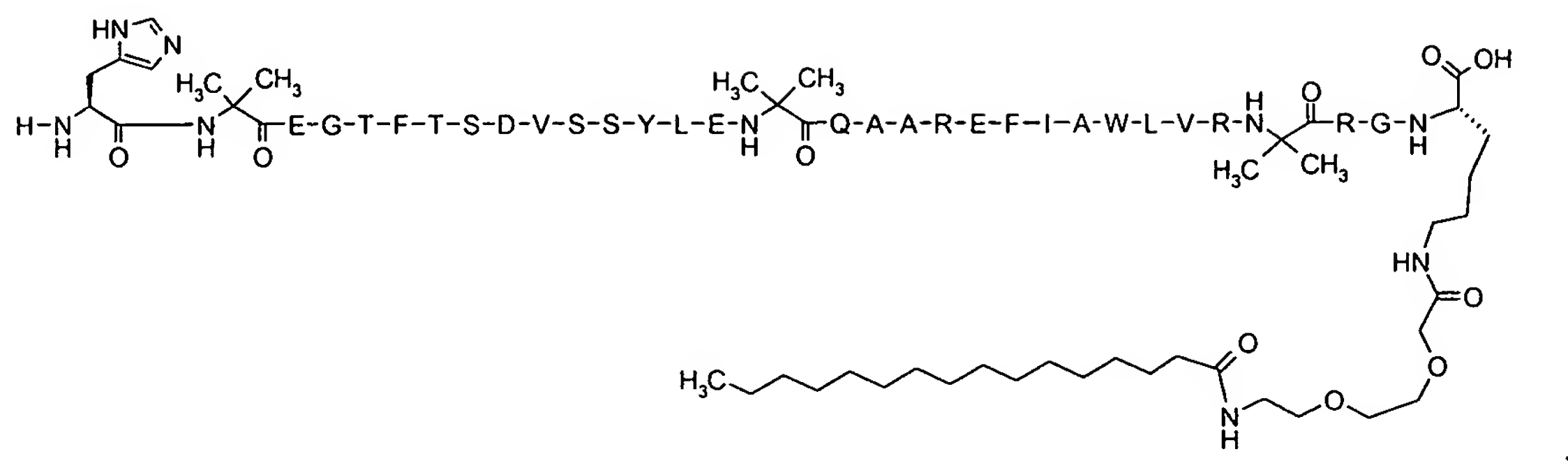


[Aib^{8,22,35},Arg^{26,34}]GLP-1-(7-37)Lys(4-(Hexadecanoylamino)-4(S)-carboxybutyryl)-OH

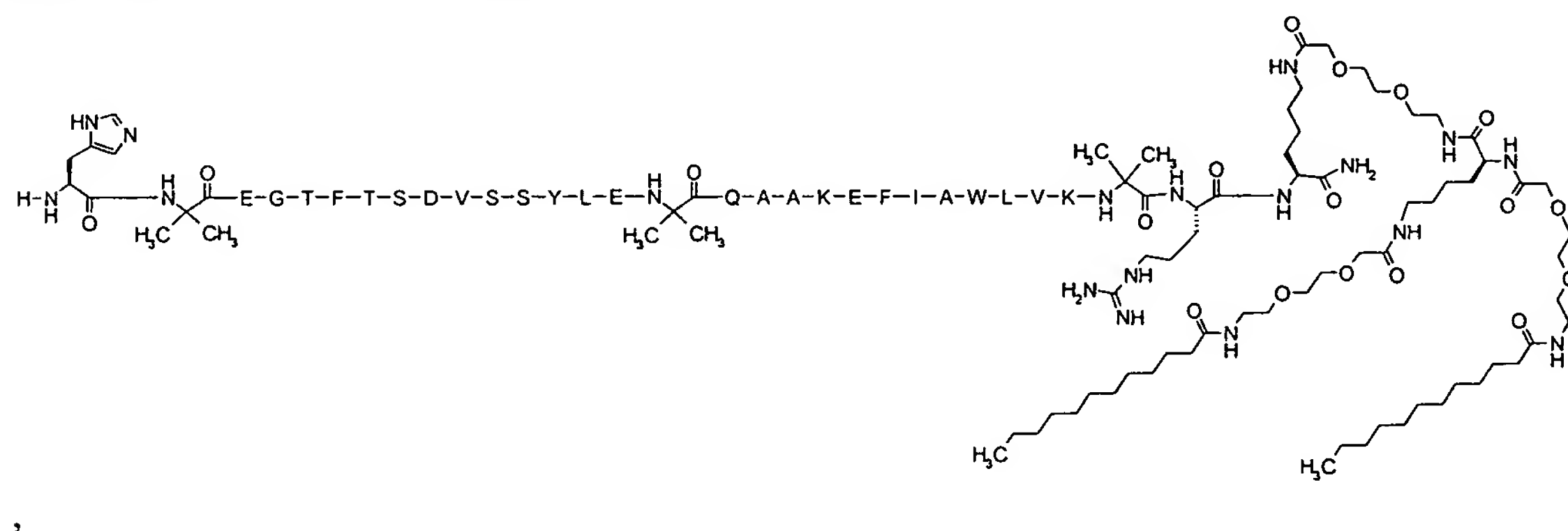


[Aib^{8,22,35},Arg^{26,34}]GLP-1-(7-37)Lys(2-(2-(2-(hexadecanoylamino)ethoxy)ethoxy)acetyl)-OH

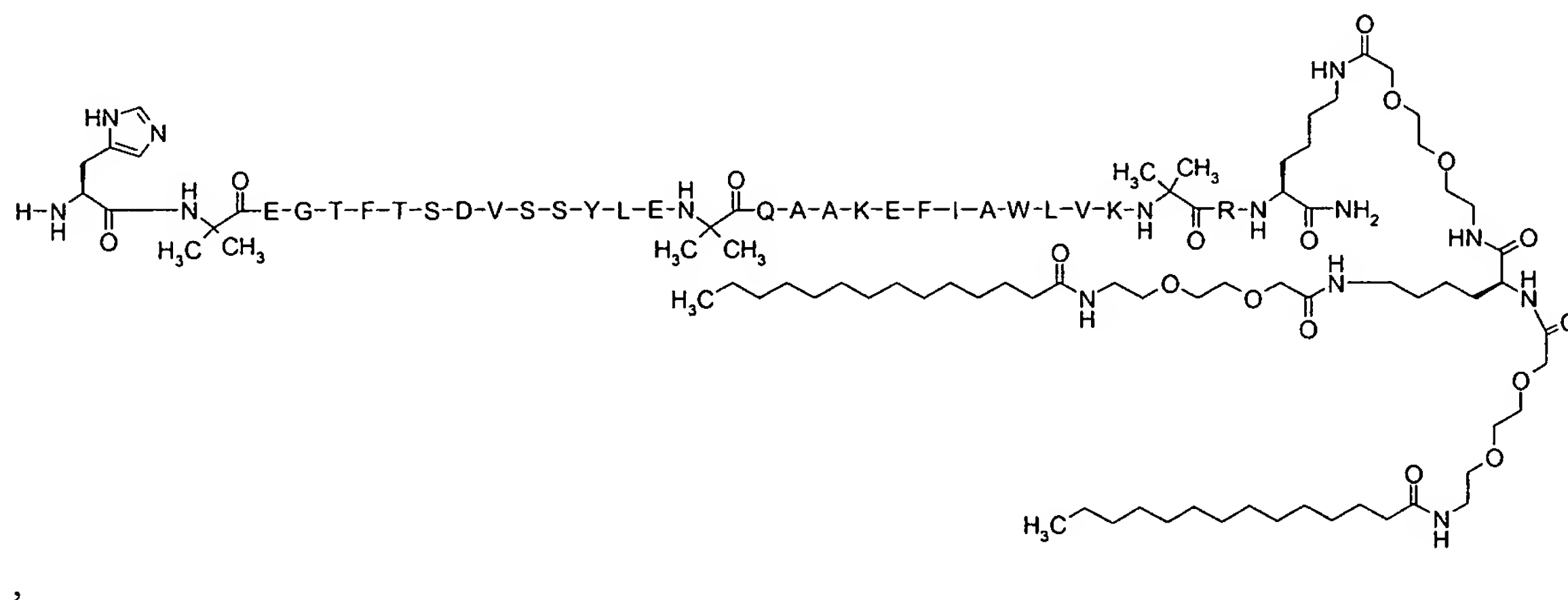
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$N^{(2,2,2)}$ -(2-[2-(2,6-(S)-Bis-{2-[2-(2-(dodecanoylamino)ethoxy)ethoxy]acetylaminohexanoylamino)ethoxy]ethoxy})
 acetyl-[Aib^{8,22,35}]GLP-1(7-37)amide



$N^{(2,2,2)}$ -(2-[2-(2,6-(S)-Bis-{2-[2-(2-(tetradecanoylamino)ethoxy)ethoxy]acetylaminohexanoylamino)ethoxy]ethoxy})
 acetyl-[Aib^{8,22,35}]GLP-1(7-37)amide



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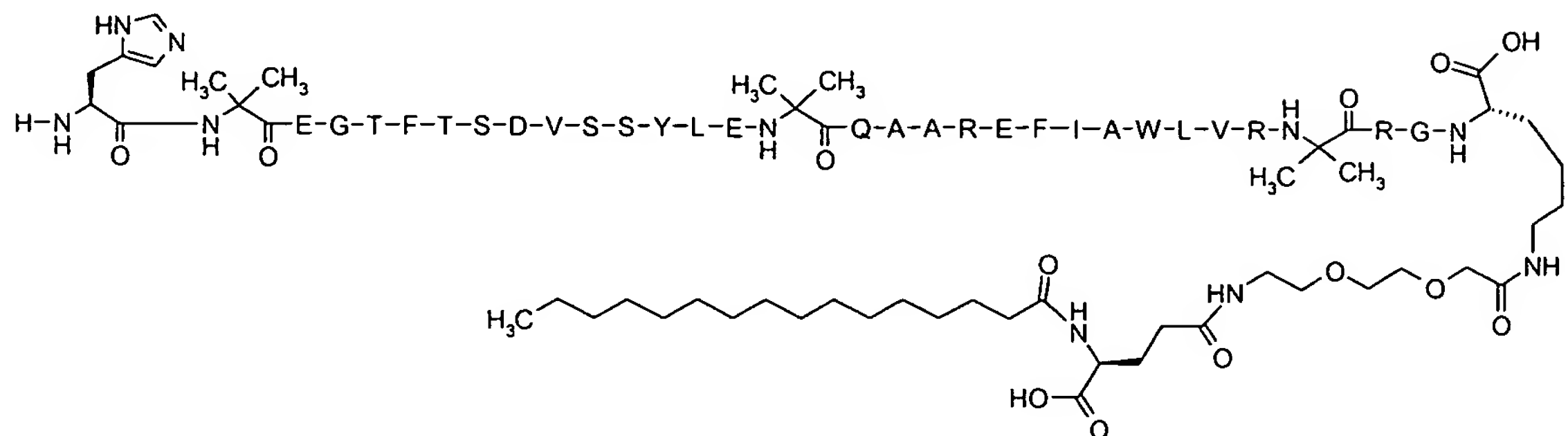
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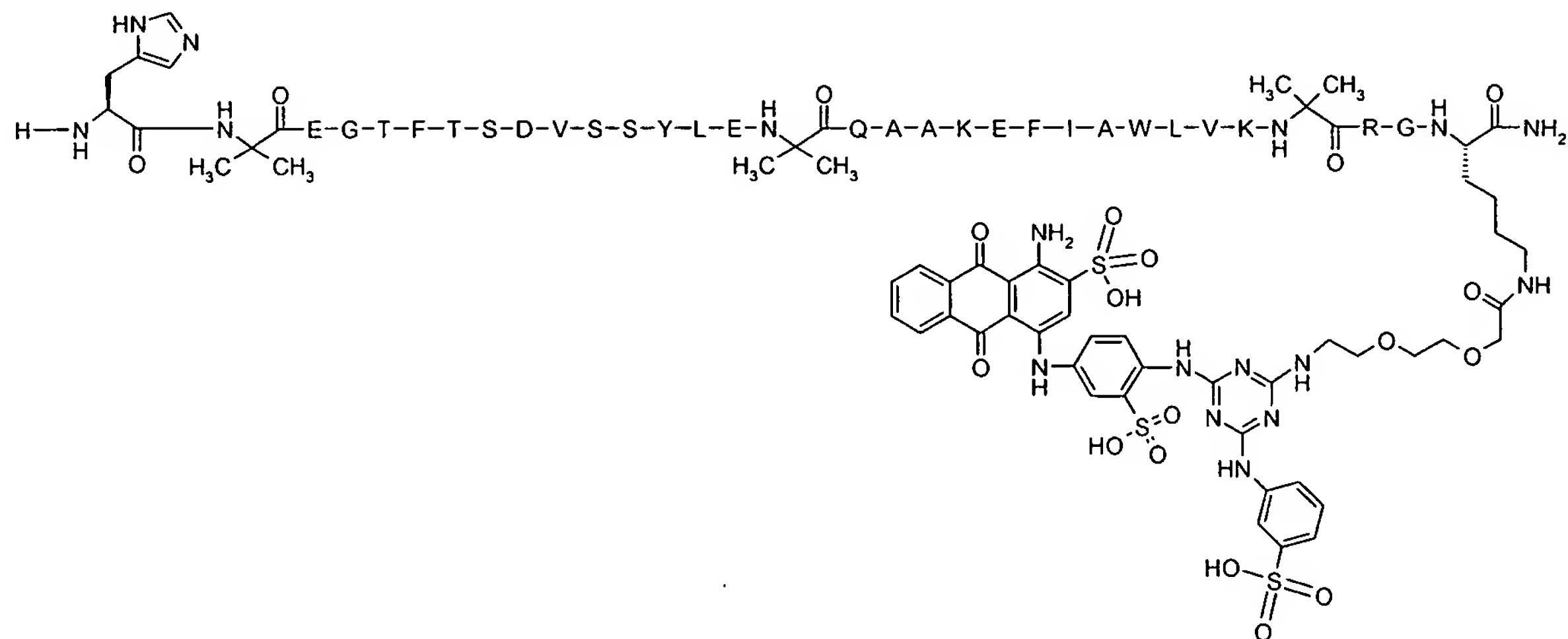
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[Aib^{8,22,35},Arg^{26,34}]GLP-1-(7-37)Lys(2-(2-(2-(4-(Hexadecanoylamino)-4(S)-carboxybutyrylamino)ethoxy)ethoxy)acetyl)-OH



,

[Aib^{8,22,35}]GLP-1(7-37)Lys((2-{2-[4-[4-(4-Amino-9,10-dioxo-3-sulfo-9,10-dihydro-anthracen-1-ylamino)-2-sulfo-phenylamino]-6-(2-sulfo-phenylamino)-[1,3,5]triazin-2-ylamino]-ethoxy}-ethoxy)-acetyl))amide



,

[Aib^{8,22,35}]GLP-1(7-37)Lys(((2-[2-(2-{2-[2-(2-{2-[2-(15-carboxypentadecanoylamino)-ethoxy]ethoxy}acetyl amino)ethoxy]ethoxy}acetyl amino)ethoxy]ethoxy}acetyl))amide

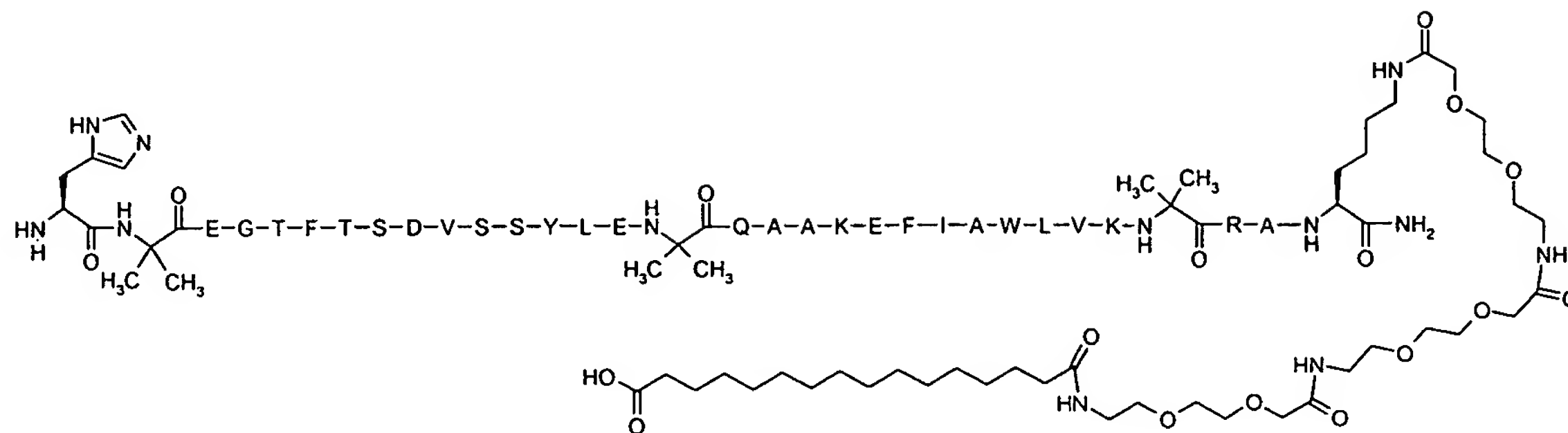
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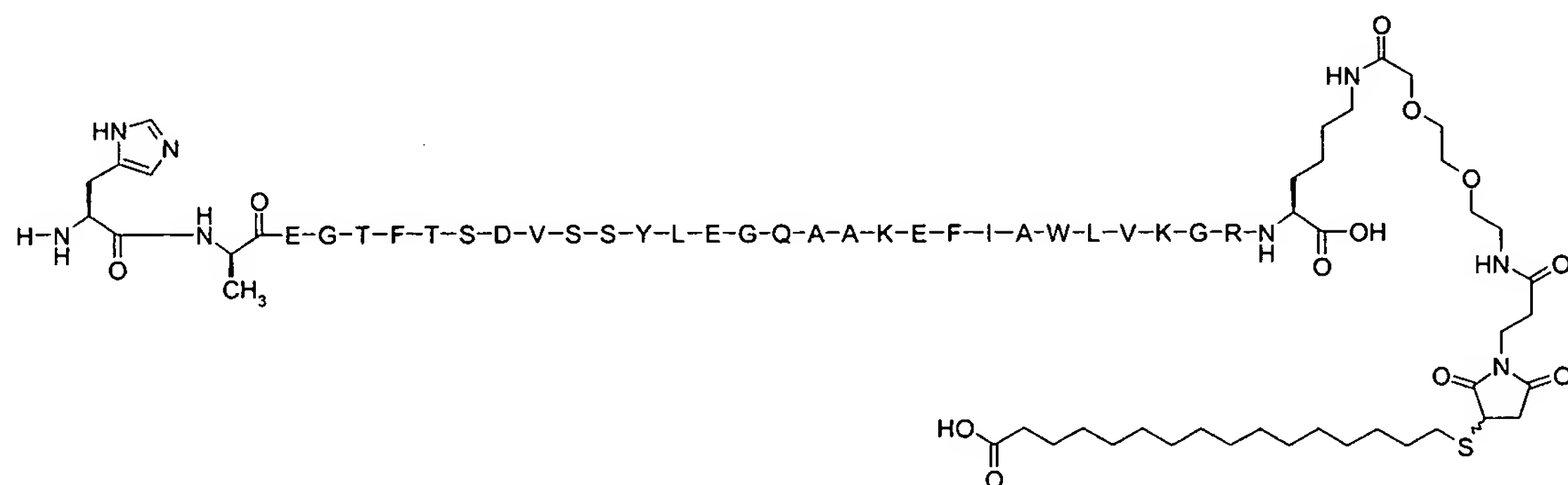


,

N^{□□□}-([2-(2-{3-[2,5-dioxo-3-(15-carboxypentadecylsulfanyl)-pyrrolidin-1-yl]-

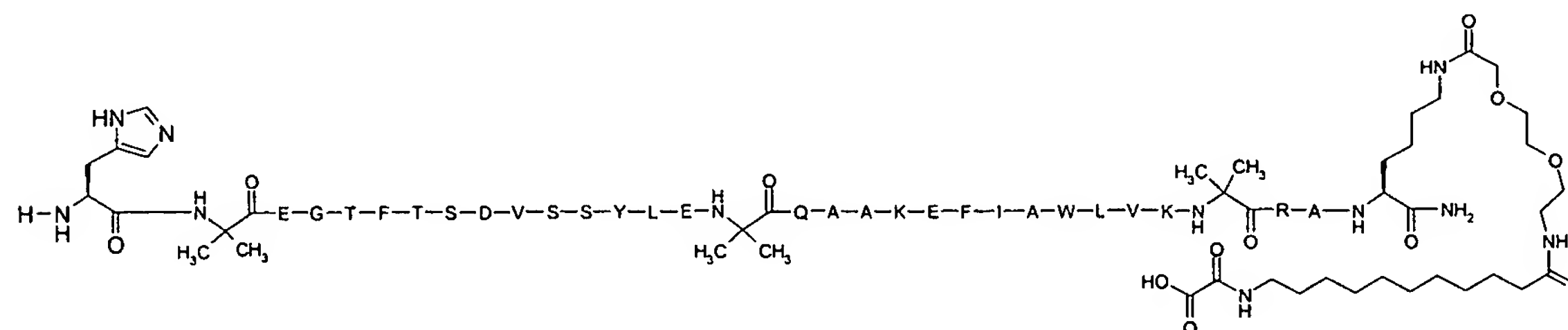
propionylamino}ethoxy)ethoxy)acetyl]-[D-Ala⁸,Lys³⁷]-GLP-1-[7-

37]amide



,

[Aib^{8,22,35},Ala³⁷]-GLP-1(7-37)Lys((2-(2-(2-(11-(oxalylamino)undecanoylamino)ethoxy)ethoxy)acetyl-
)))amide



,

[Aib^{8,22,35},Ala³⁷]-GLP-1(7-37)Lys({2-[2-(2-{2-[2-(2-(15-carboxy-pentadecanoylamino)-
ethoxy]ethoxy} acetylamino)ethoxy]ethoxy} acetyl)amide

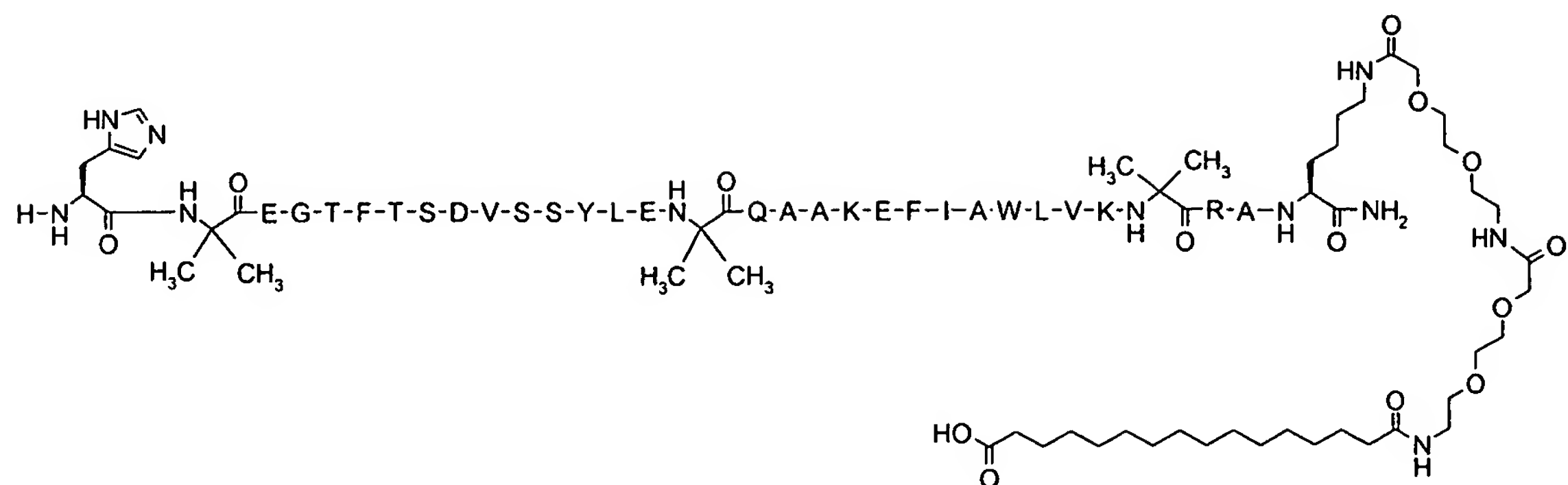
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Applicants: Lau et al.

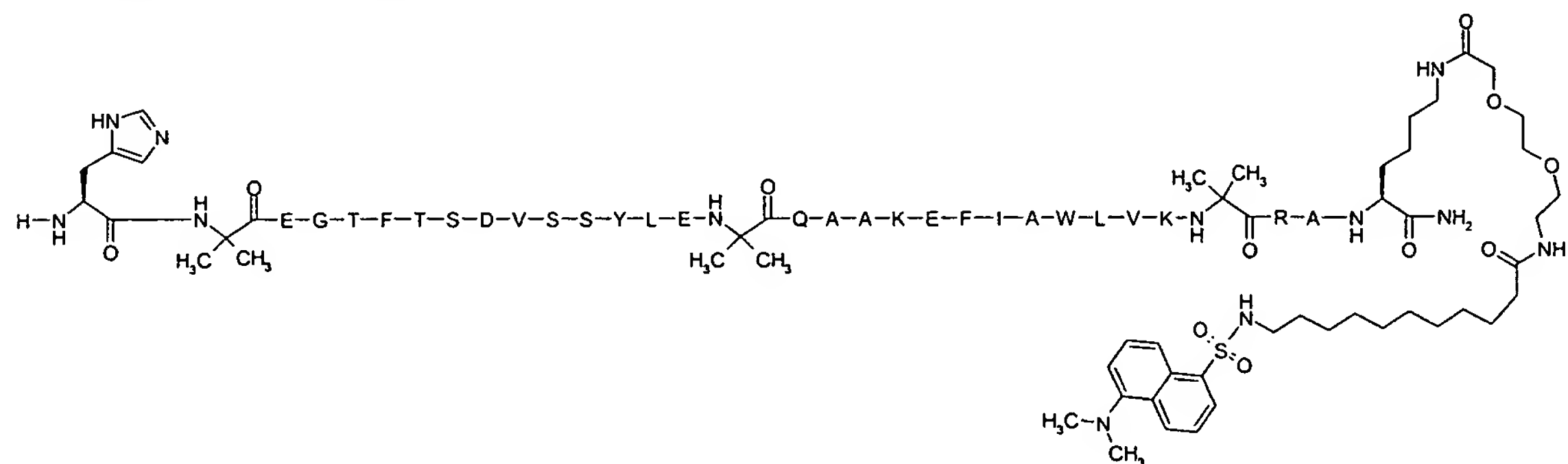
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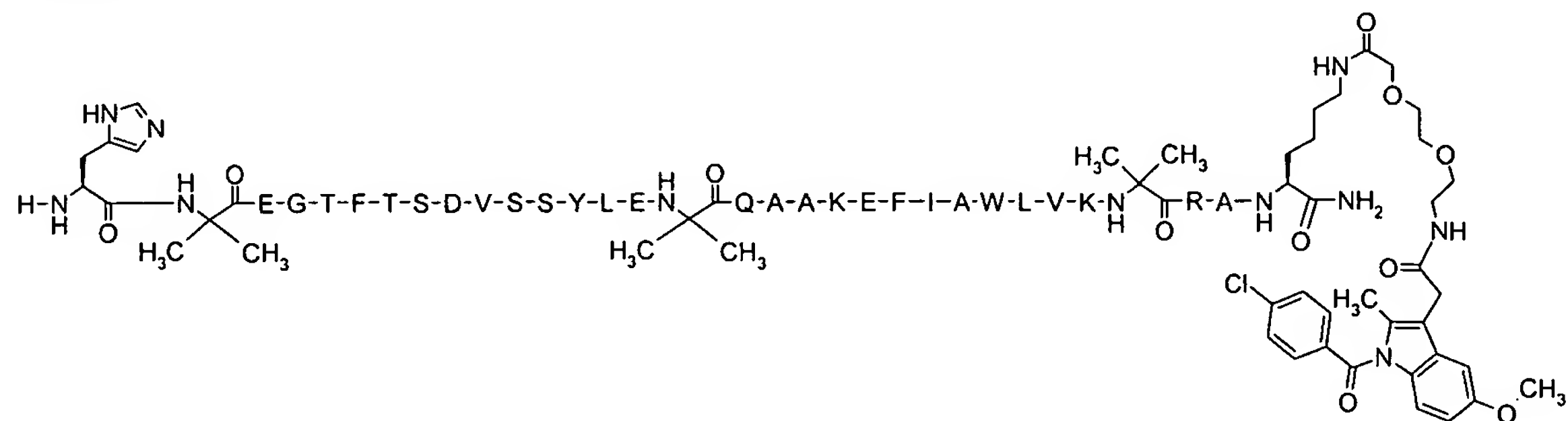
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[Aib^{8,22,35},Ala³⁷]-GLP-1(7-37)Lys((2-{2-[11-(5-Dimethylaminonaphthalene-1-sulfonylamino)undecanoylamino]ethoxy}ethoxy)acetyl)amide



[Aib^{8,22,35},Ala³⁷]-GLP-1(7-37)Lys(((2-(2-{2-[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetyl)amino}ethoxy)ethoxy)acetyl))amide



[Aib⁸,Arg^{26,34},Glu^{22,23,30}]-GLP-1 H(7-37)Lys(2-(2-(2-(octadecanoylamino)ethoxy)ethoxy)acetyl)amide

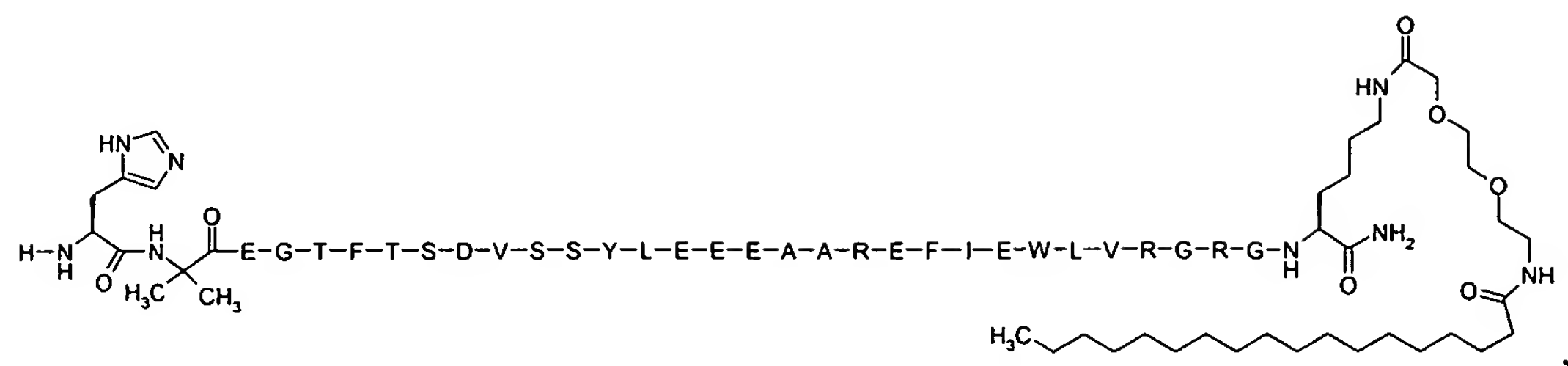
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Applicants: Lau et al.

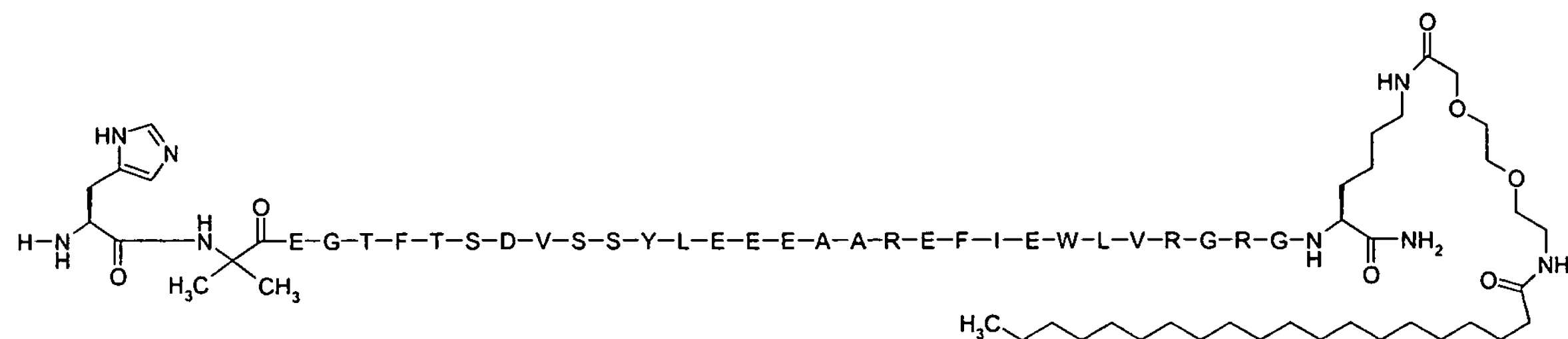
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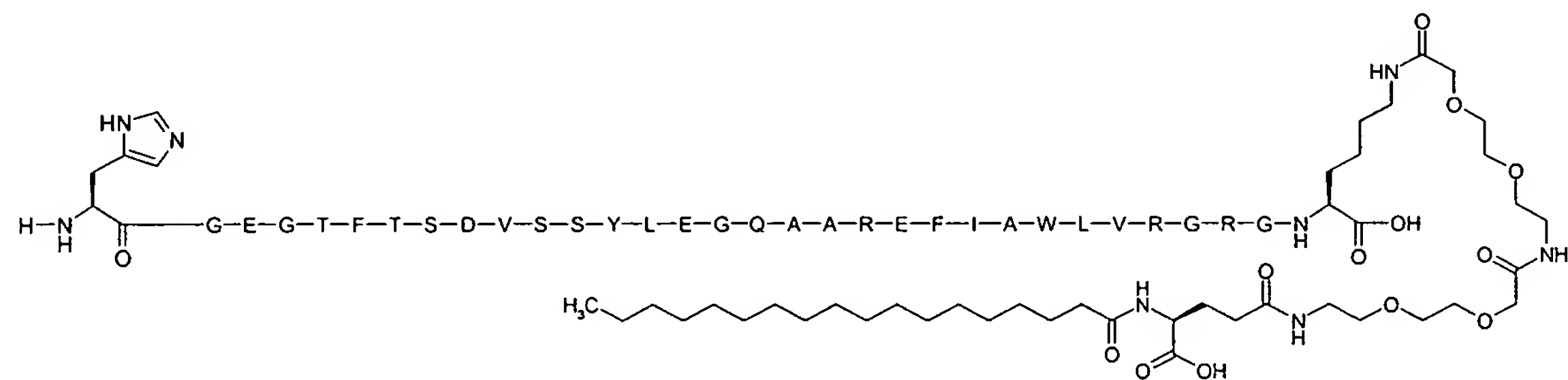


[Aib⁸, Arg^{26,34}, Glu^{22,23,30}]GLP-1(7-37)Lys(2-(2-(2-(eicosanoylamino)ethoxy)ethoxy)acetyl)amide



,

[Gly⁸, Arg^{26,34}] GLP-1 H-(7-37)Lys(2-(2-(2-(2-(2-(2-(4-(octadecanoylamino)-4(S)-carboxybutyrylamino)ethoxy)ethoxy)acetyl)ethoxy)ethoxy)acetyl)-OH



,

[Aib⁸, Arg^{26,34}]GLP-1 (7-37)Lys{2-(2-(2-(2-[2-(2-(octadecanoylamino)ethoxy)ethoxy]acetyl)ethoxy)ethoxy)acetyl)}-OH

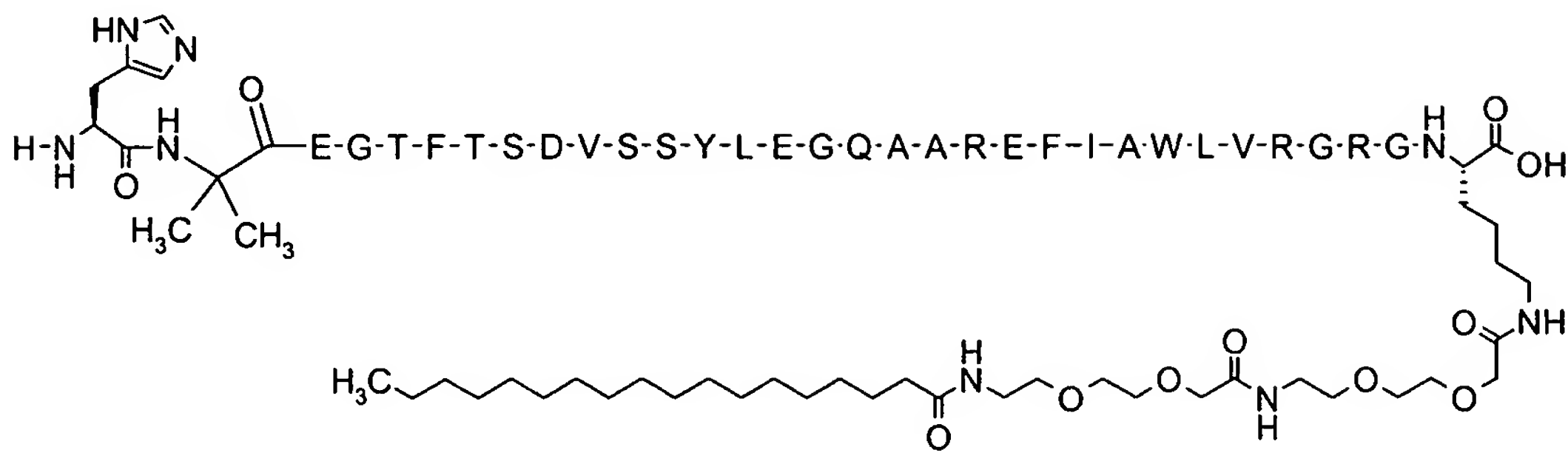
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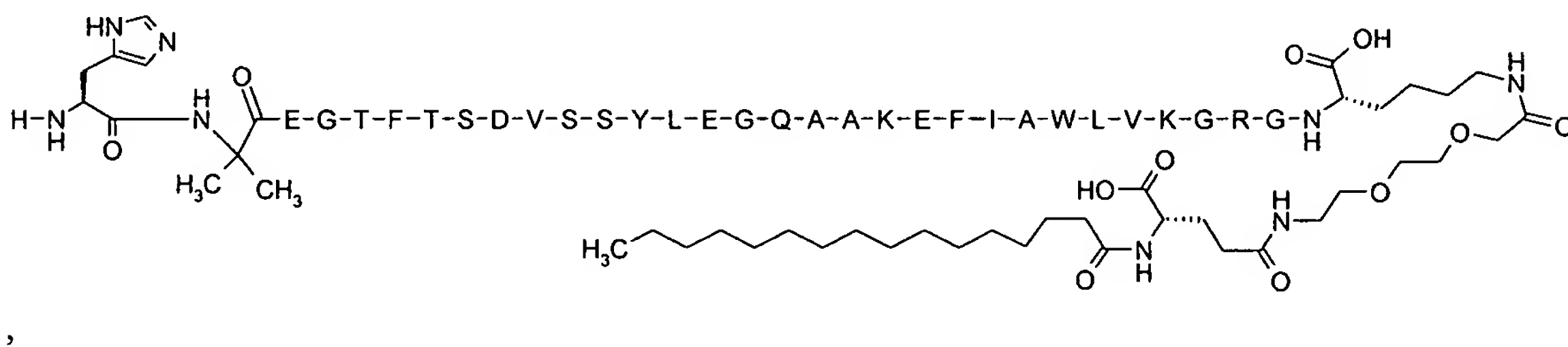
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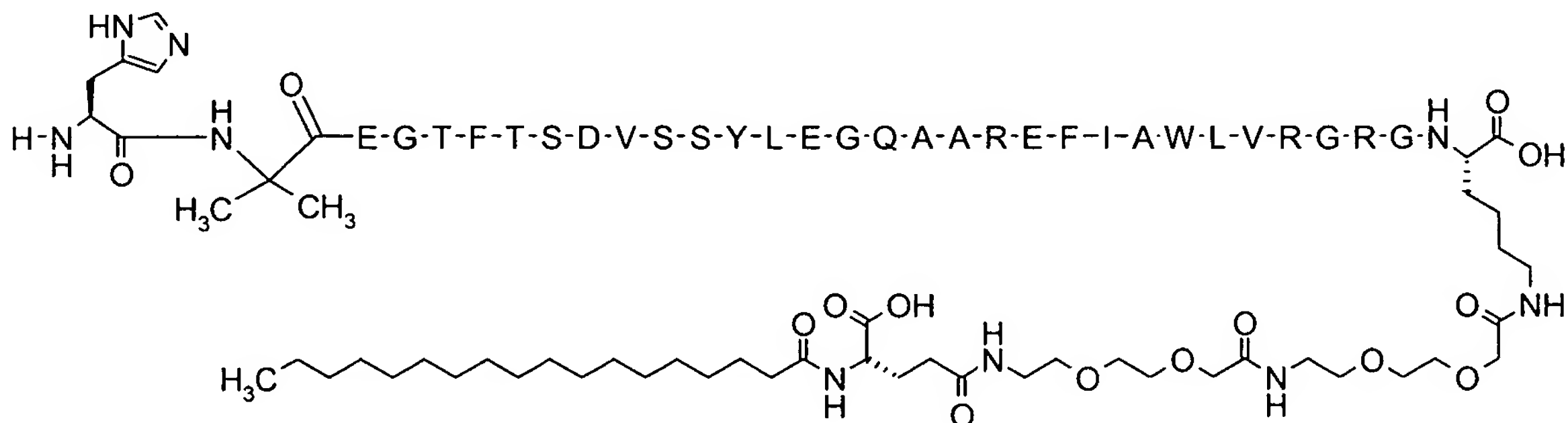
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[Aib⁸] -GLP-1-(7-37)Lys (2-(2-(2-(4-(Hexadecanoylamino)-4(S)-carboxybutyrylamino)ethoxy)ethoxy)acetyl)-OH



[Aib⁸,Arg^{26,34}] GLP-1(7-37) Lys{2-(2-(2-(2-[2-(2-(4-(octadecanoylamino)-4-carboxybutyrylamino)ethoxy)ethoxy]acetyl)ethoxy)ethoxy)acetyl))-OH



[Aib⁸,Arg^{26,34}] GLP-1 (7-37)Lys{2-(2-(2-(2-[2-(2-(17-carboxyheptanoylamino)ethoxy)ethoxy]acetyl)ethoxy)ethoxy)acetyl))-OH

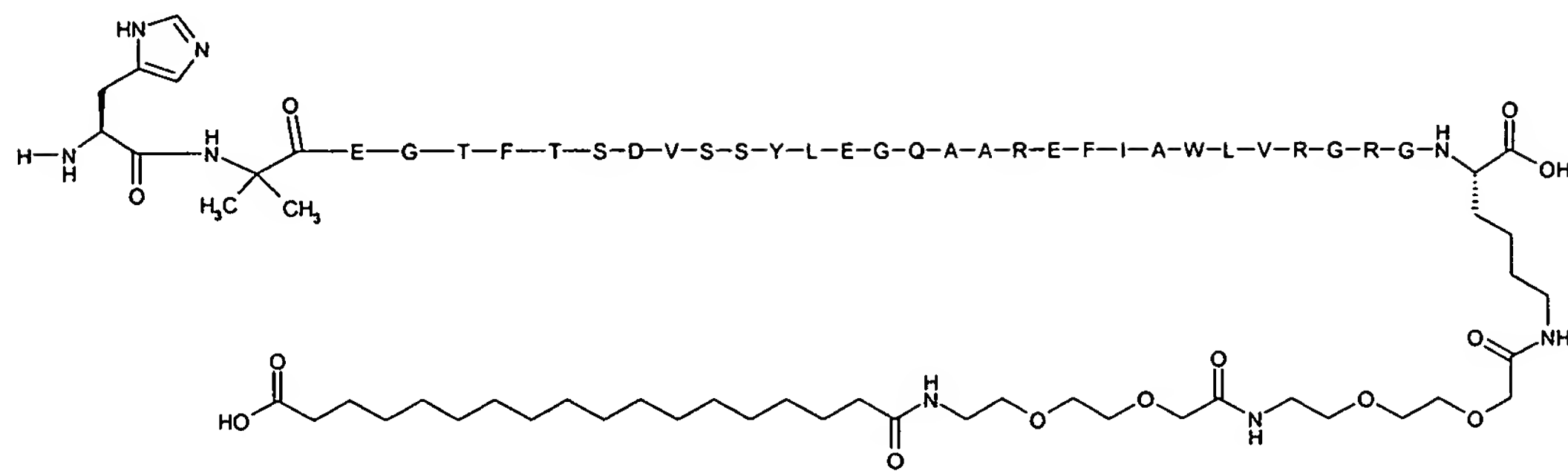
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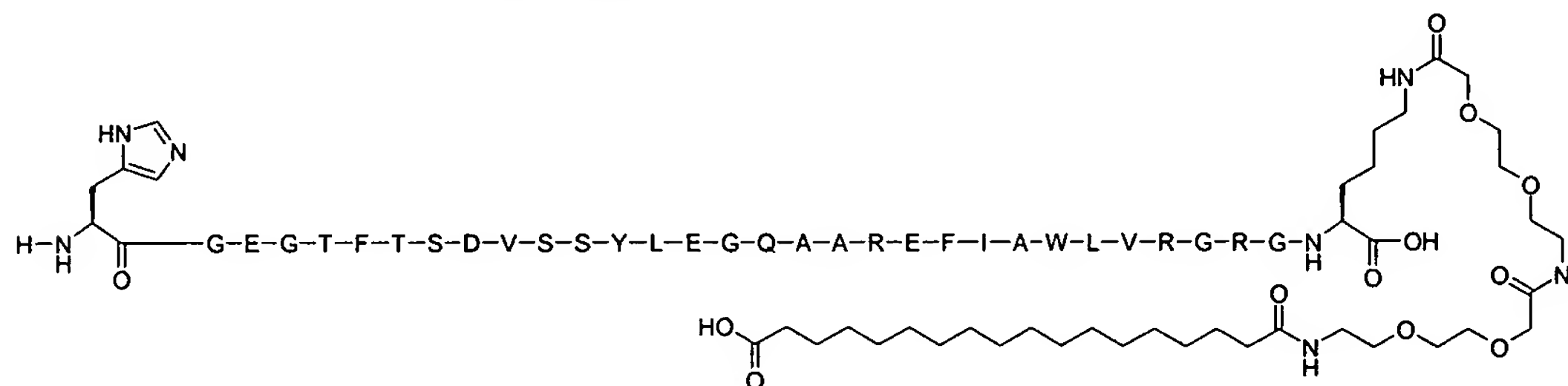
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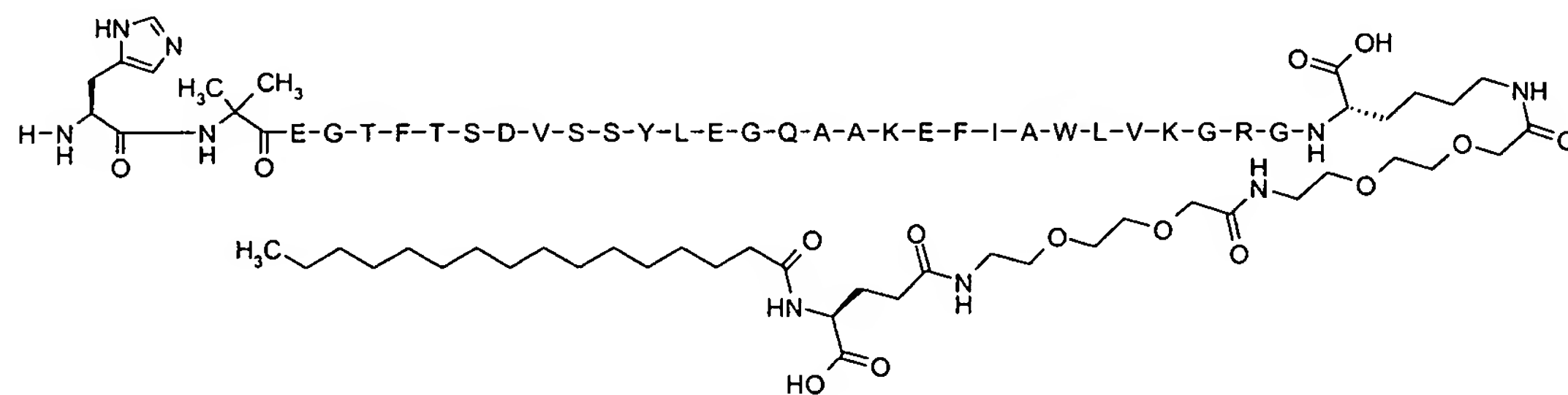
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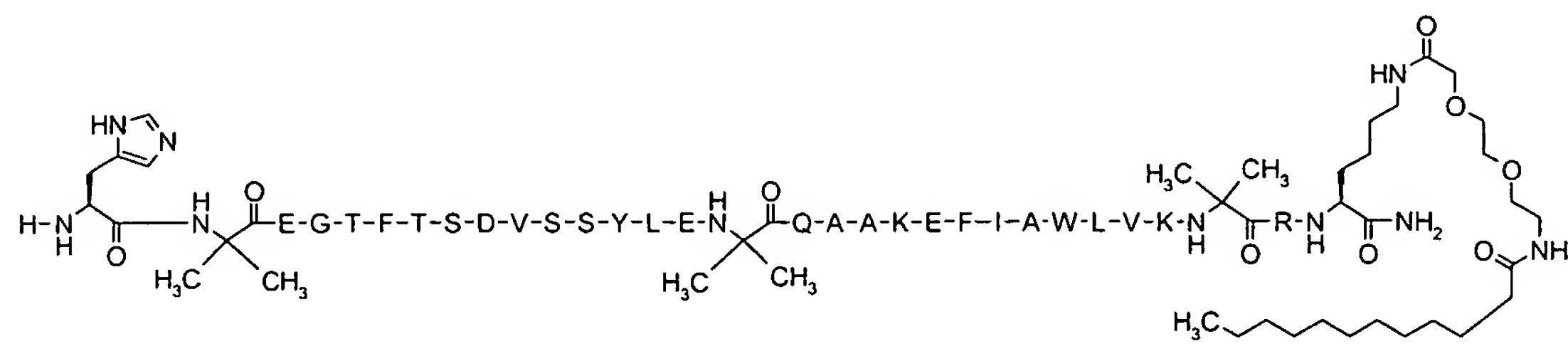
[Gly⁸, Arg^{26,34}] GLP1-(7-37) Lys{2-(2-(2-(2-[2-(2-(17-carboxyheptadecanoylamino)ethoxy)ethoxy]acetyl)ethoxy)ethoxy)acetyl)}-OH



[Aib⁸]GLP-1-(7-37)Lys(2-(2-(2-(2-(2-(4-(Hexadecanoylamino)-4(S)-carboxybutyrylamino)ethoxy)ethoxy)acetyl)amino)ethoxy)ethoxy)acetyl)-OH



N^{ε37}-(2-(2-(2-(dodecanoylamino)ethoxy)ethoxy)acetyl)-[Aib^{8,22,35}Lys³⁷] GLP-1 H(7-37)-amide



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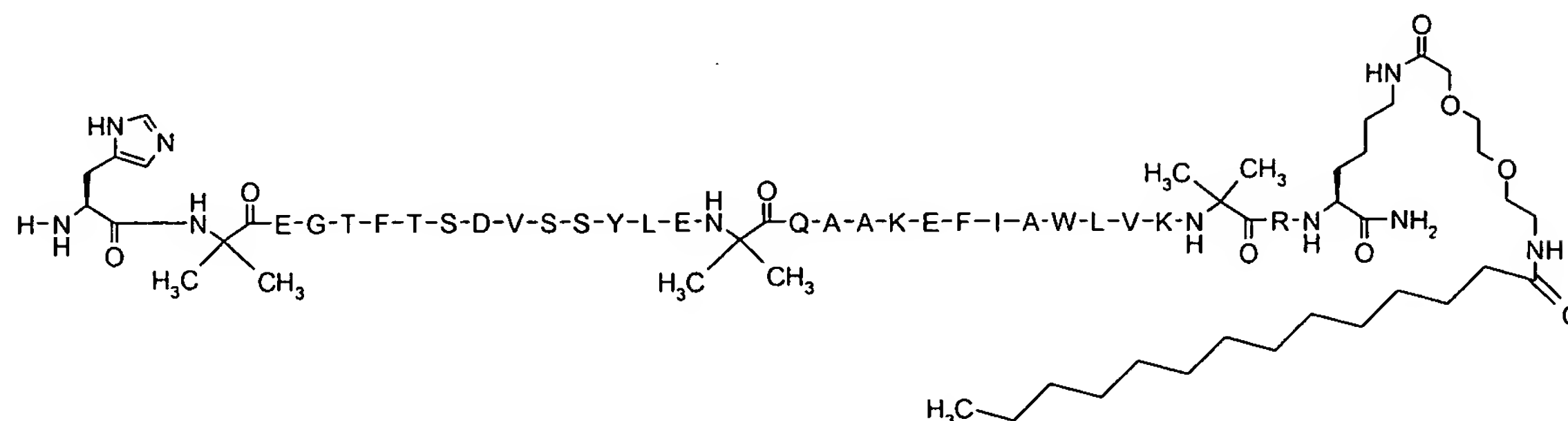
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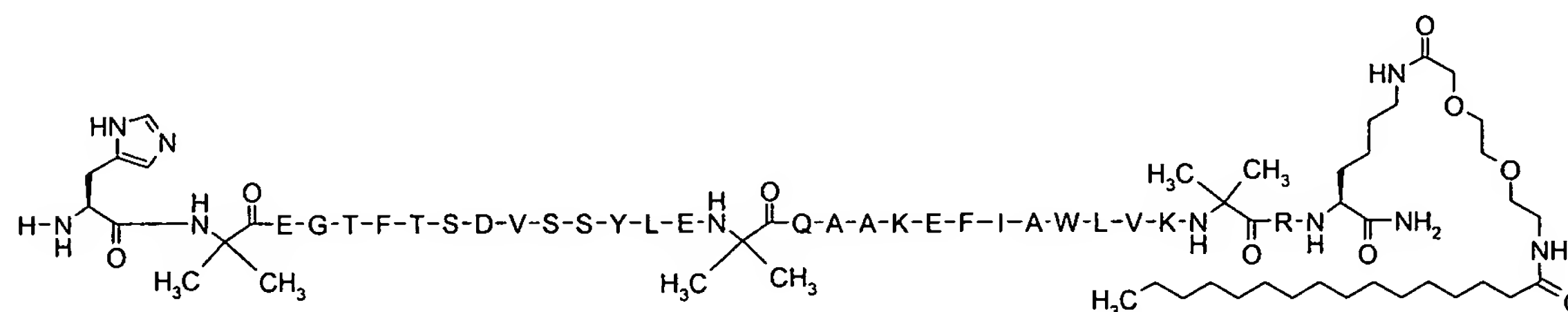
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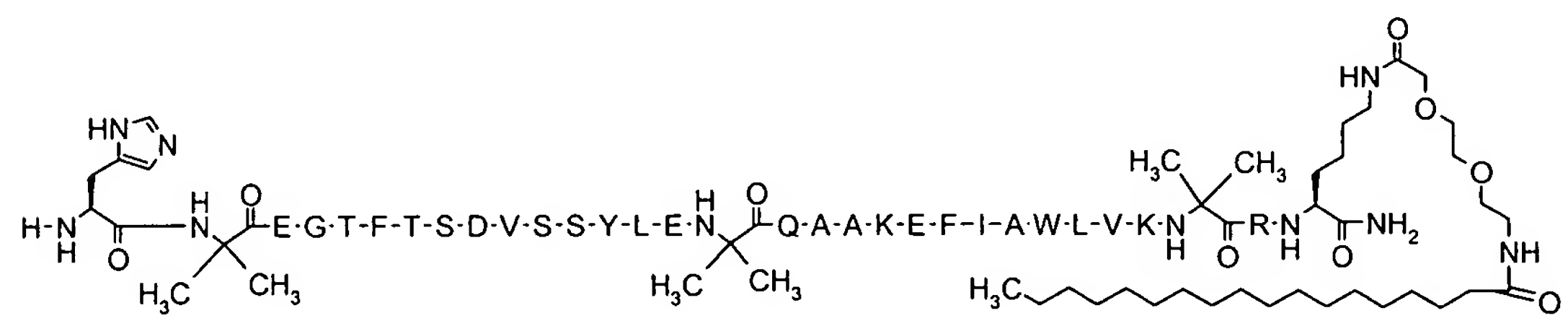
$N^{\epsilon 37}$ -(2-(2-(2-(tetradecanoylamino)ethoxy)ethoxy)acetyl)-[Aib^{8,22,35}Lys³⁷] GLP-1 H(7-37)-amide



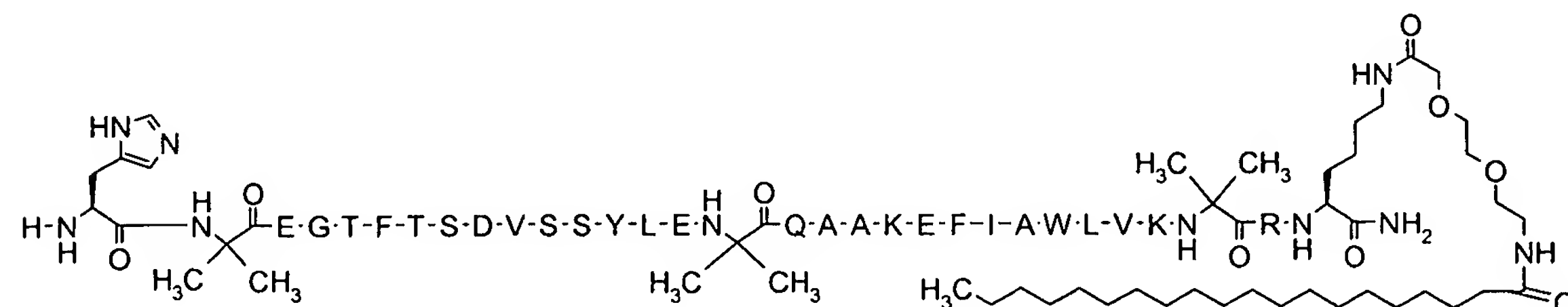
$N^{\epsilon 37}$ -(2-(2-(2-(hexadecanoylamino)ethoxy)ethoxy)acetyl)-[Aib^{8,22,35}Lys³⁷] GLP-1 (7-37)-amide



$N^{\epsilon 37}$ -(2-(2-(2-(octadecanoylamino)ethoxy)ethoxy)acetyl)-[Aib^{8,22,35}Lys³⁷] GLP-1 (7-37)-amide

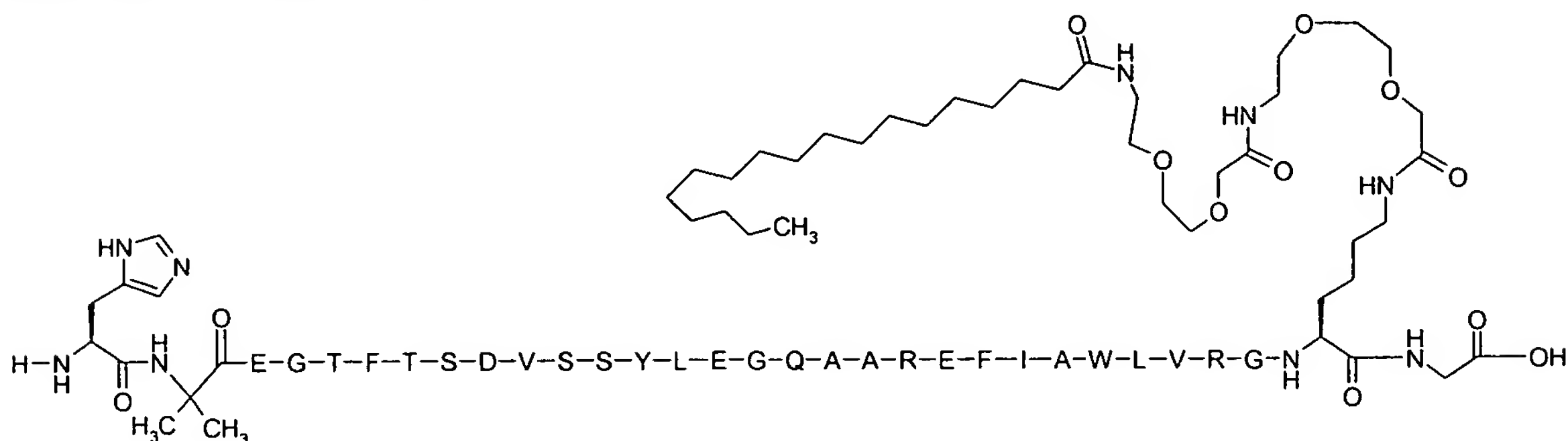


$N^{\epsilon 37}$ -(2-(2-(2-(eicosanoylamino)ethoxy)ethoxy)acetyl)-[Aib^{8,22,35}Lys³⁷] GLP-1(7-37)-amide

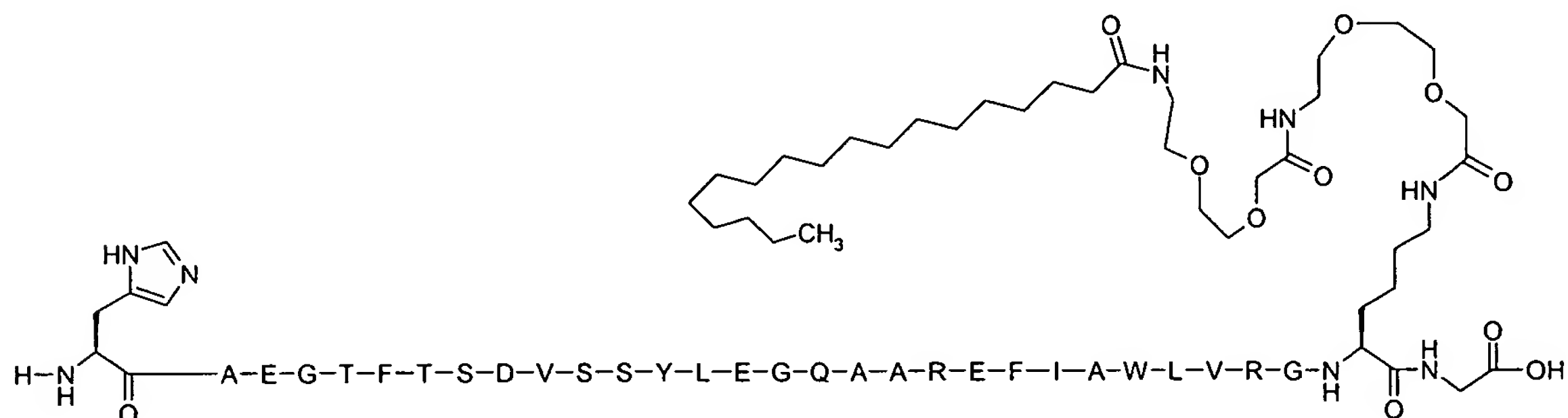


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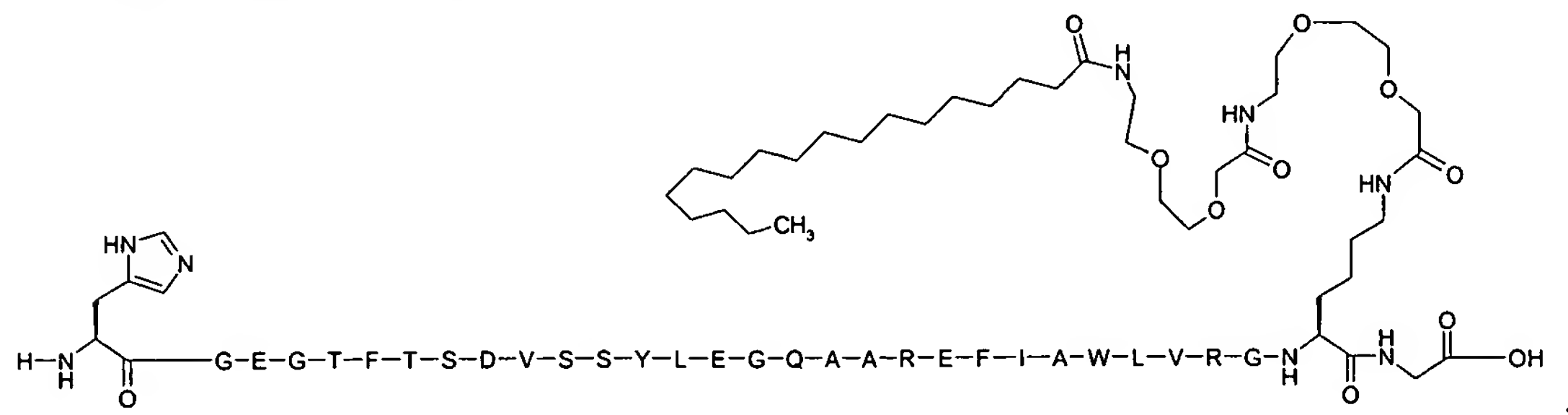
[Aib⁸,Arg^{26,34},Lys³⁶]GLP-1-(7-37)-OH



OH



[Gly⁸,Arg^{26,34},Lys³⁶]GLP-1-(7-37)-OH

butyrylamino)ethoxy)ethoxy)acetyl)) [Aib^{8,22,35}, Lys³⁷] GLP-1-(7-37)-OH

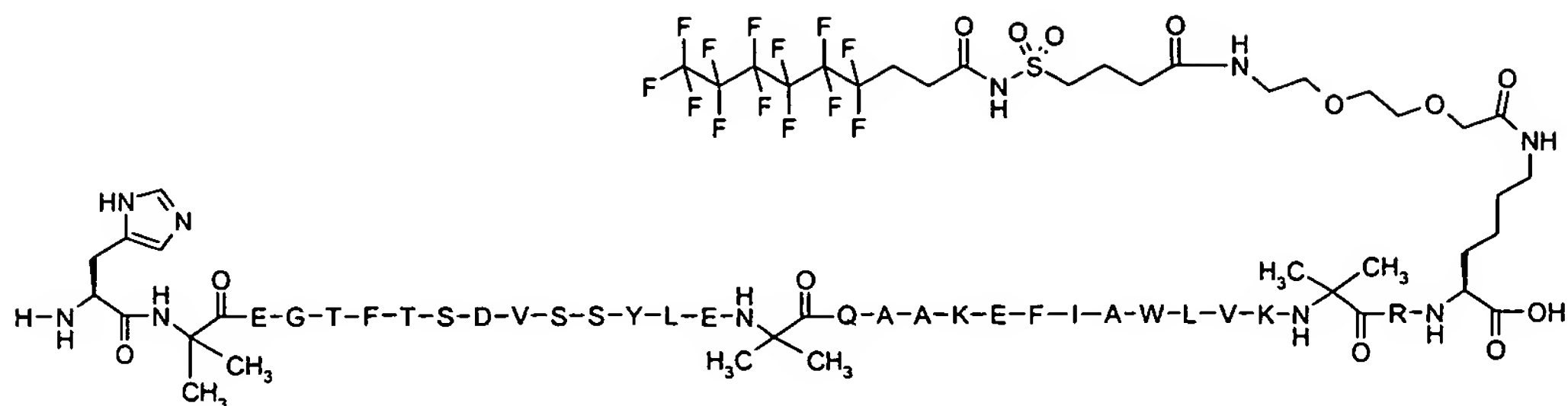
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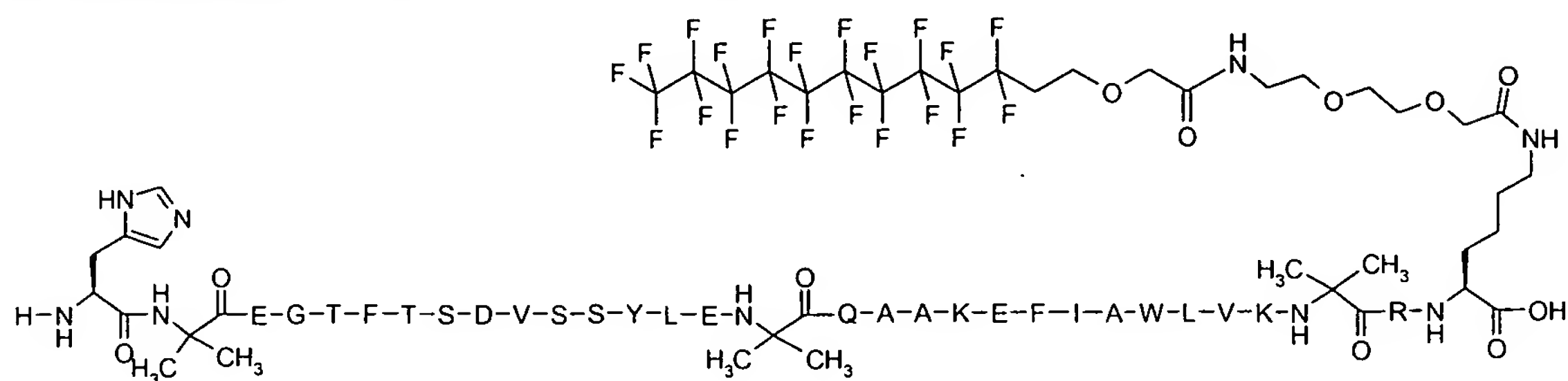
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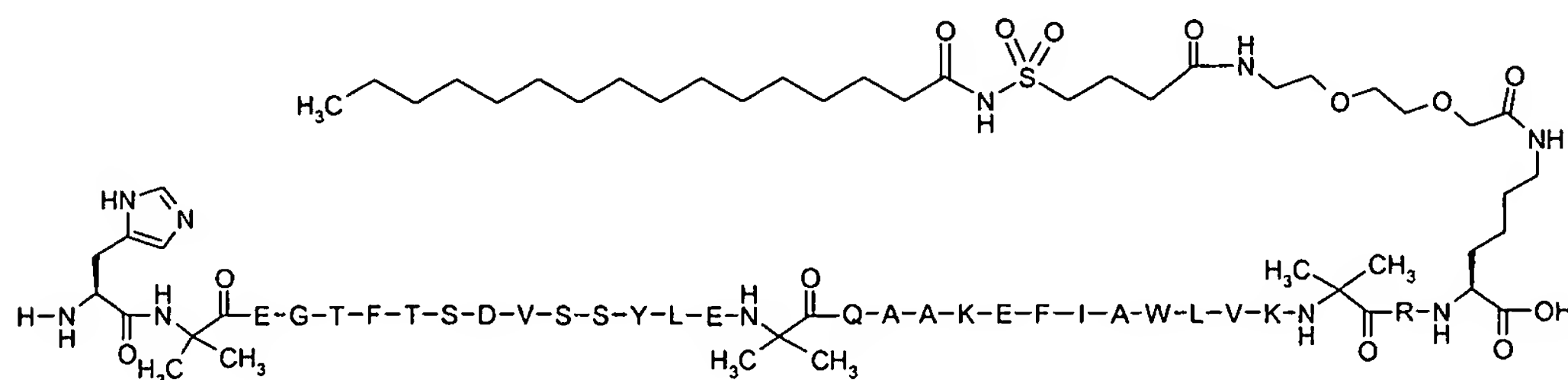


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ethoxy)acetyl][Aib^{8,22,35},Lys³⁷]GLP-1-(7-37)-OH



N^{ε37}-(2-(2-(2-(4-(hexadecanoylsulfamoyl)butyryl)amino)ethoxy)ethoxy)acetyl][Aib^{8,22,35},Lys³⁷]GLP-1-(7-37)-OH



[Arg^{26,34}]GLP-1(7-37)Lys({2-(2-(2-(2-[2-(2-(octadecanoylamino)ethoxy)ethoxy]acetyl)amino)ethoxy)ethoxy)acetyl)))-OH

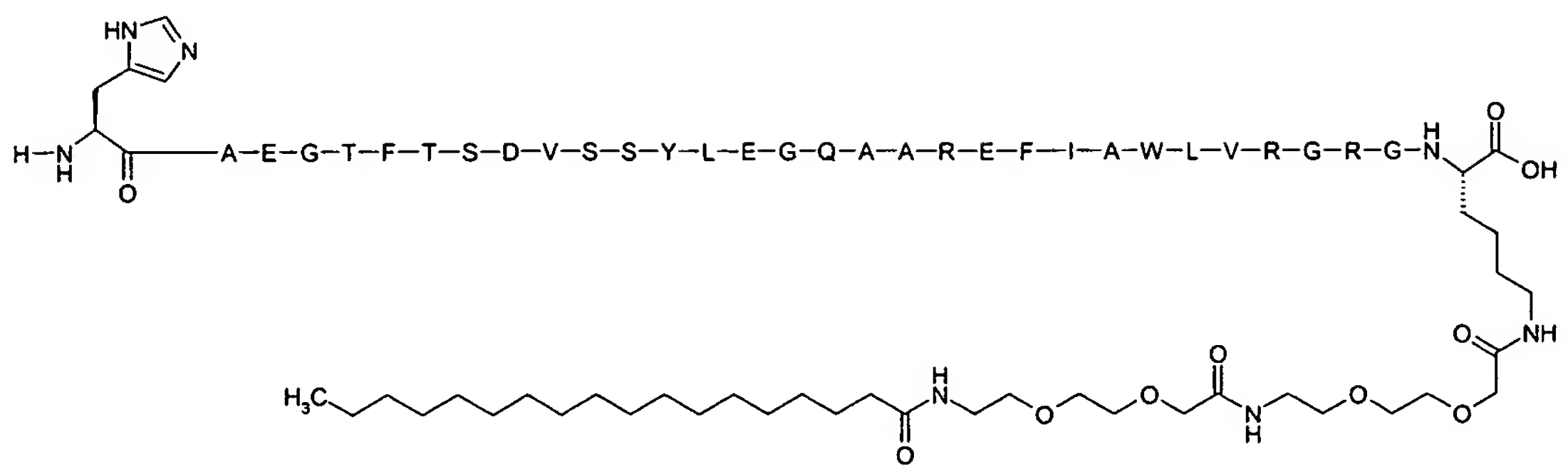
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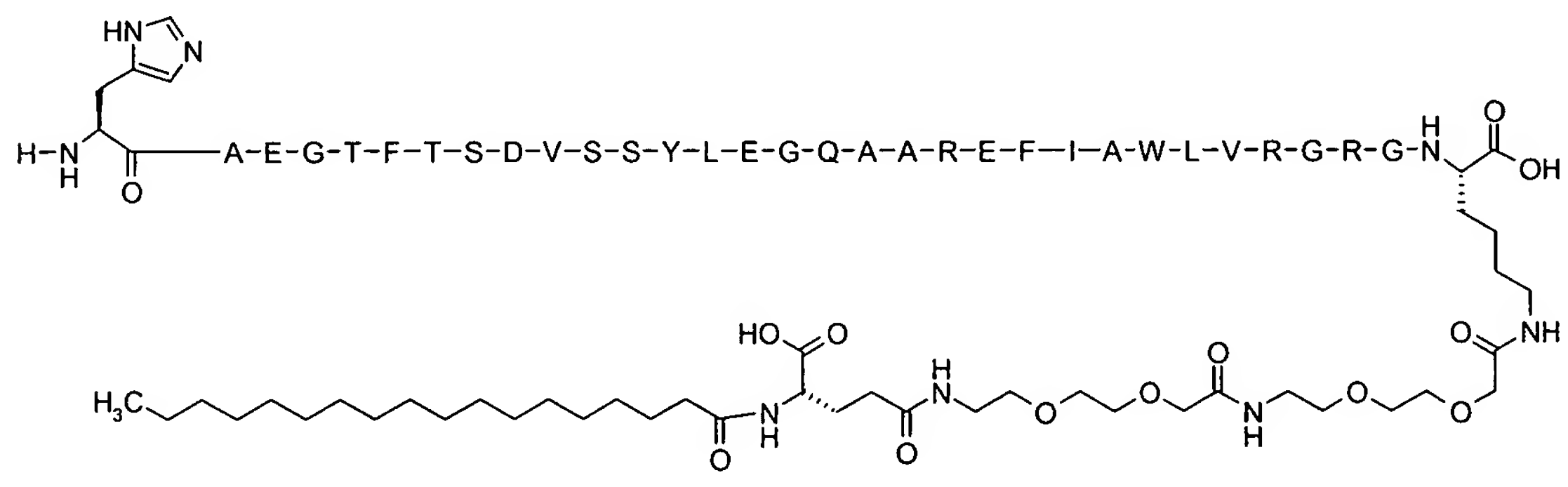
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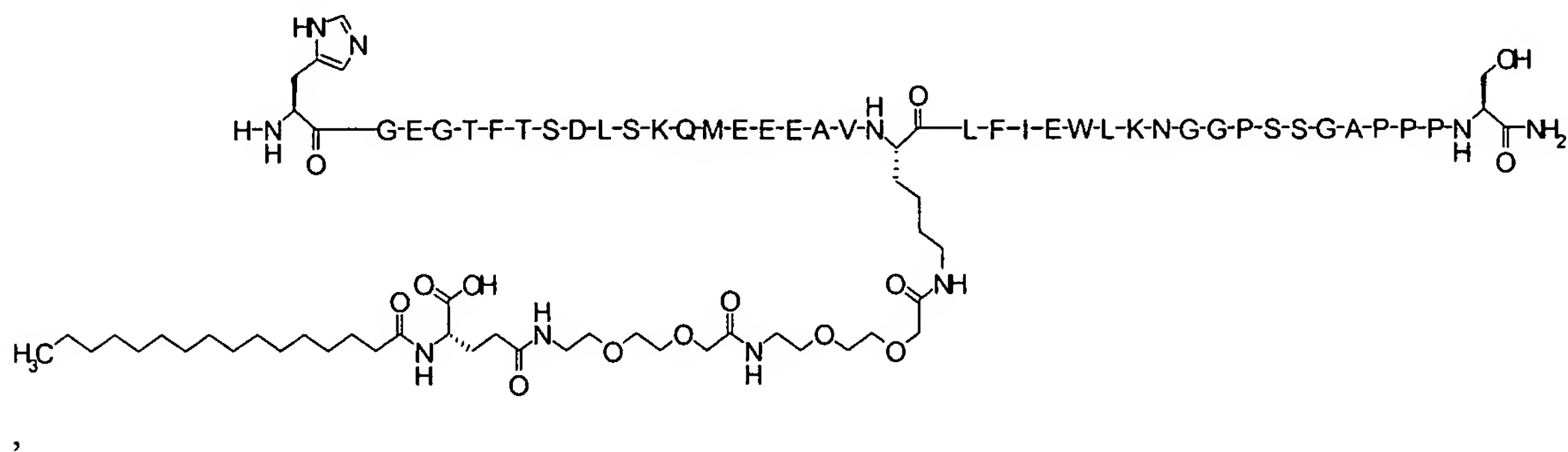
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[Arg^{26,34}] GLP-1(7-37)Lys{2-(2-(2-(2-[2-(2-(4-(octadecanoylamino)-4-carboxybutyrylamino)ethoxy)ethoxy]acetylamin)ethoxy)ethoxy)acetyl)}-OH

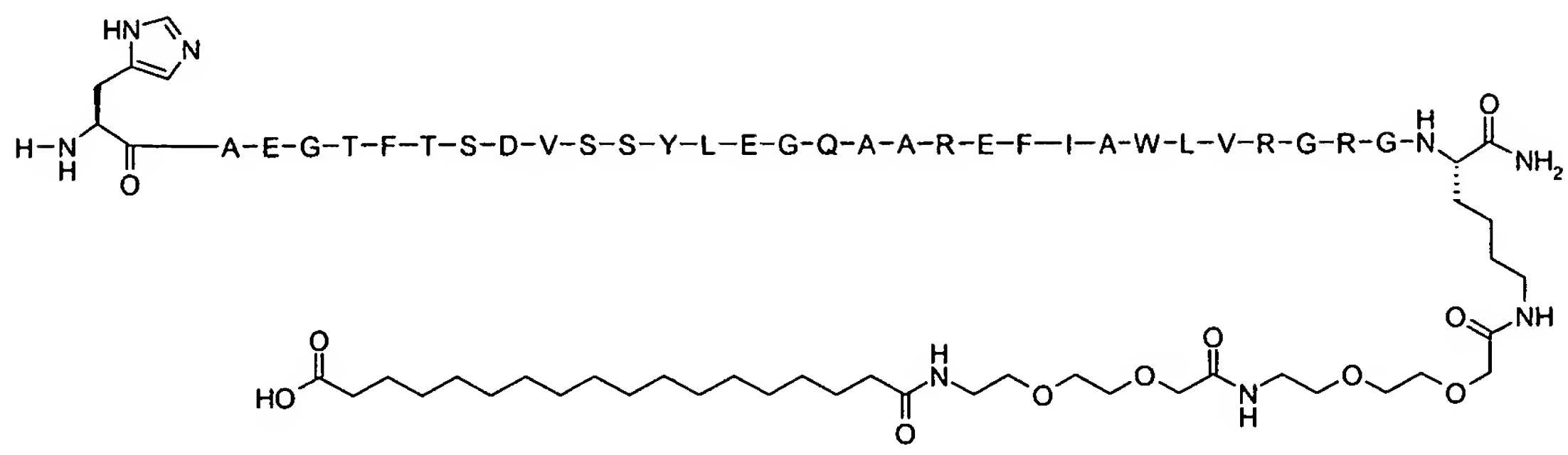


N^{□□}-{2-(2-(2-(2-[2-(2-(4-(hexadecanoylamino)-4-carboxybutyrylamino)ethoxy)ethoxy]acetylamin)ethoxy)ethoxy)acetyl)}-exendin(1-39)

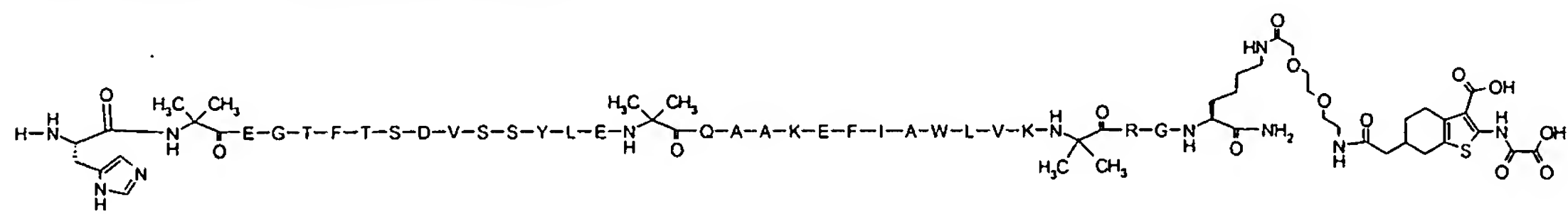


[Ala⁸, Arg^{26,34}]GLP-1(7-37)Lys((2-[2-((2-oxalylamino-3-carboxy-2,4,5,6,7-tetrahydrobenzo[b]thiophen-6-yl-acetylamin)ethoxy]ethoxyacetyl) amide

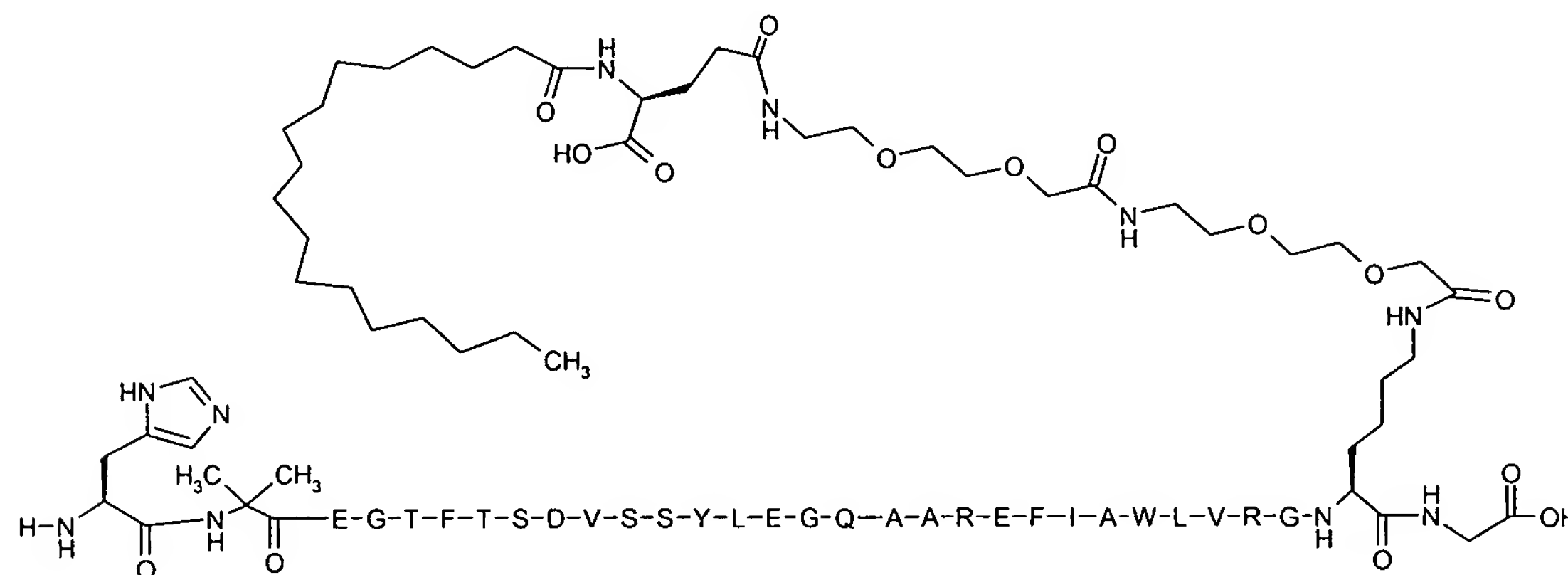
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[Aib^{8,22,35}]GLP-1(7-37)Lys((2-[2-((2-oxalylamino-3-carboxy-2-4,5,6,7-tetrahydro-benzo[b]thiophen-6-yl-acetylamino))ethoxy]ethoxyacetyl) amide



N^{ε36}-(2-(2-(2-(2-(2-(2-(4-(octadecanoylamino)-4(S)-carboxybutyrylamino)ethoxy)ethoxy)acetylamino)ethoxy)ethoxy)acetyl)-[Aib⁸,Arg^{26,34},Lys³⁶]GLP-1-(7-37)-OH



N^{ε36}-(2-(2-(2-(2-(2-(2-(4-(octadecanoylamino)-4(S)-carboxybutyrylamino)ethoxy)ethoxy)acetylamino)ethoxy)ethoxy)acetyl)-[Gly⁸,Arg^{26,34},Lys³⁶]GLP-1-(7-37)-OH

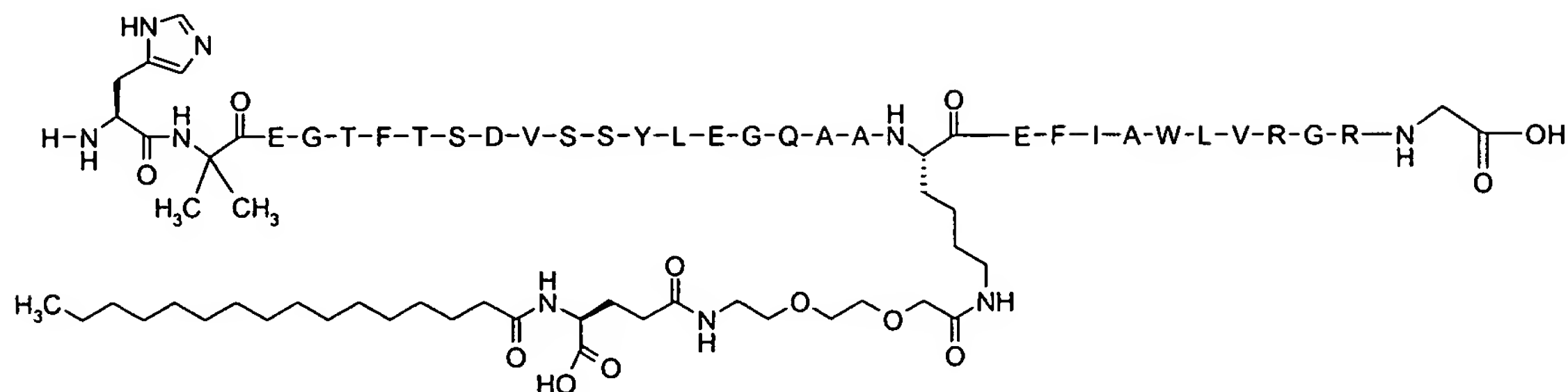
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acetyl-[Aib^{8,22,35},Lys³⁷]GLP-1-(7-37)-NH₂ethoxy)acetyl amino)ethoxy]ethoxy)acetyl-[Aib^{8,22,35},Lys³⁷]GLP-1-(7-37)-NH₂

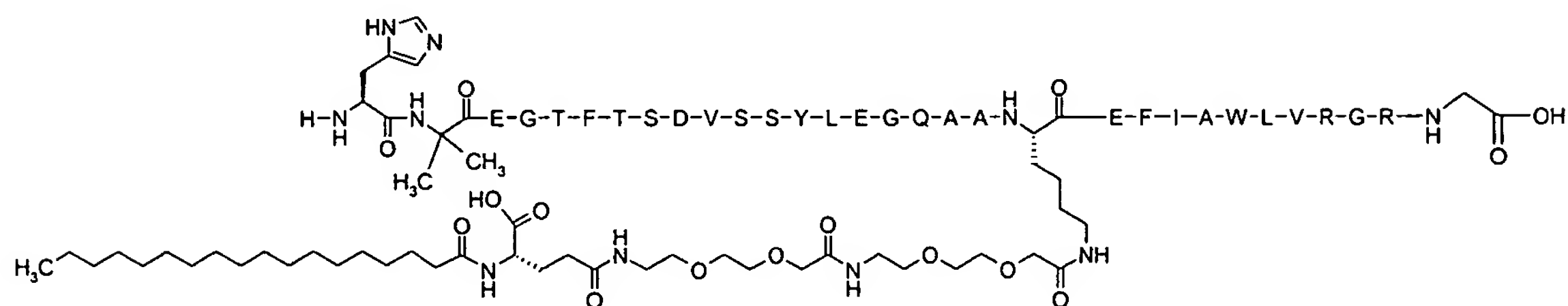
N^{□□□}-(2-(2-(2-(4-(Hexadecanoylamino)-4(S)-carboxybutyrylamino)

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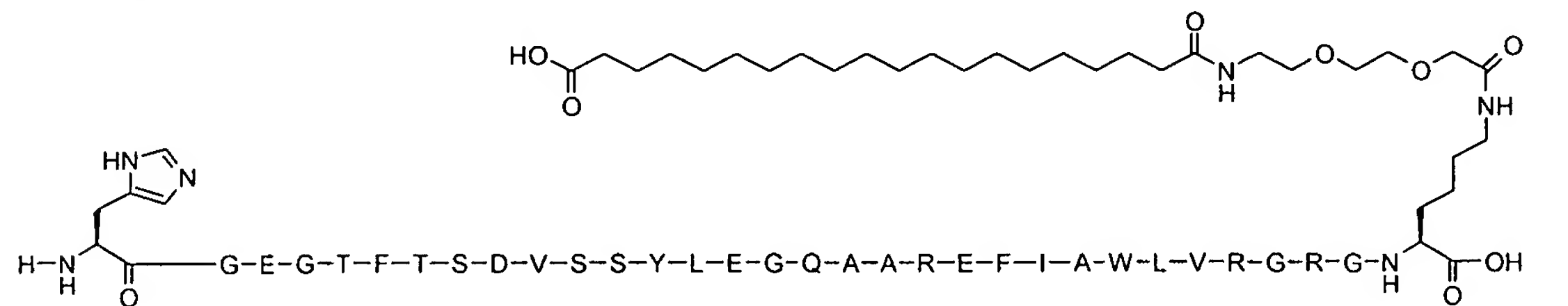
ethoxy)ethoxy)acetyl)-[Aib⁸,Arg³⁴]GLP-1-(7-37)-
 -OH



,
 N^{□□□}-2-(2-2-(2-(2-(2-(4-(Octadecanoylamino)-4(S)-
 carboxybutyrylamino)ethoxy)ethoxy)acetylaminomethoxy)ethoxy)acetyl-
 [Aib⁸,Arg³⁴]GLP-1-(7-37)-OH



,
 [Gly⁸,Arg^{26,34}]GLP-1(7-37)Lys(2-(2-(19-(carboxy)nonadecanoylamino)ethoxy)ethoxy)acetyl)-OH



[Gly⁸,Arg^{26,34}]GLP-1(7-37)Lys((2-(2-(17-(carboxy)heptadecanoylamino)ethoxy)ethoxy)acetyl))-OH

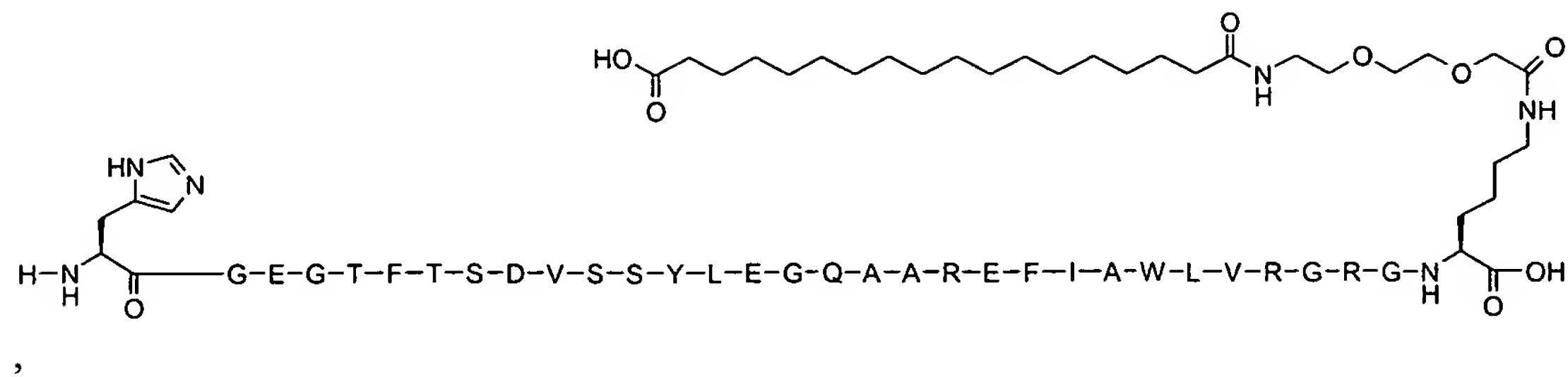
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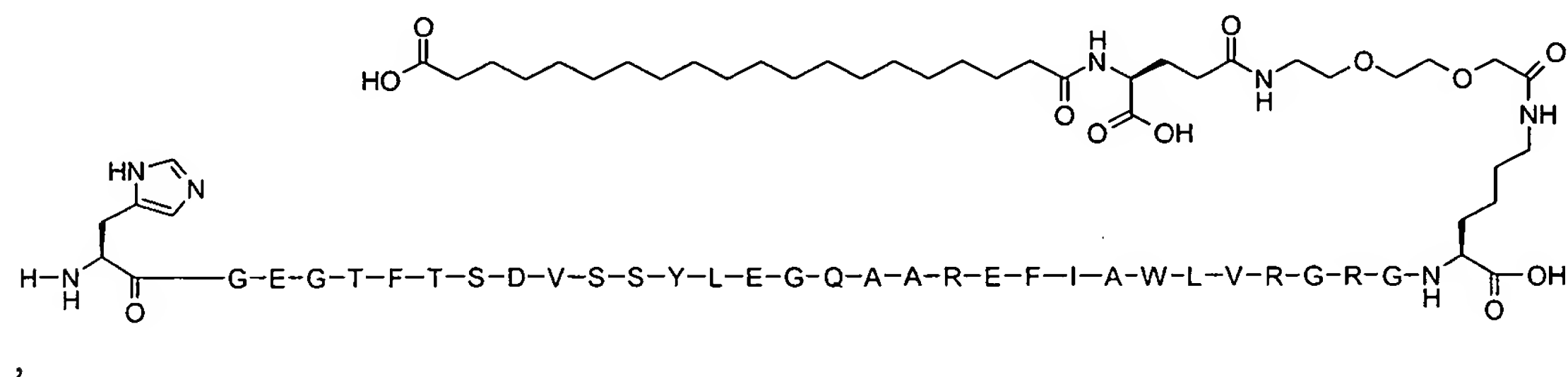
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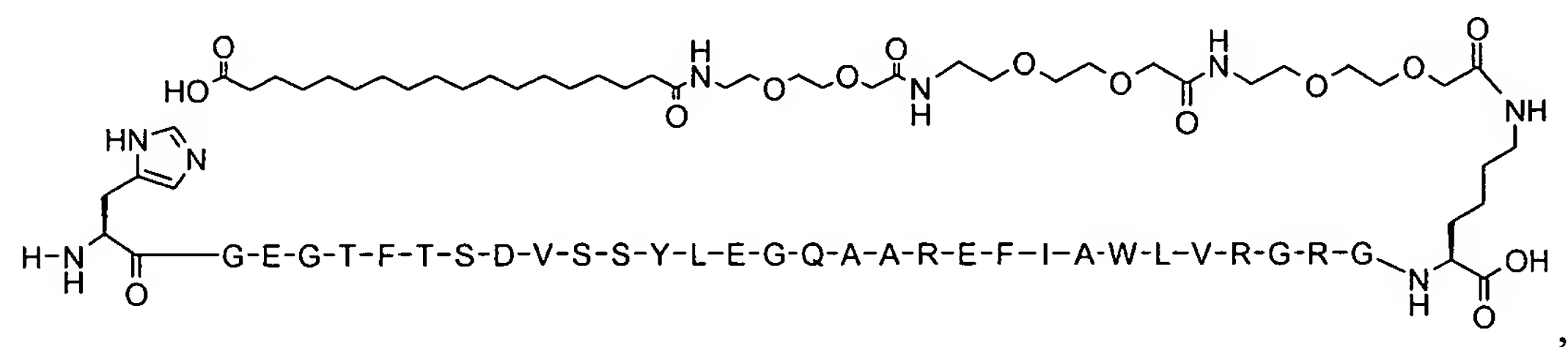
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[Gly⁸, Arg^{26,34}]GLP-1(7-37)Lys(2-(2-(2-(4-(19-(carboxy)nonadecanoylamino)-4-carboxybutyrylamino)ethoxy)ethoxy)acetyl)-OH

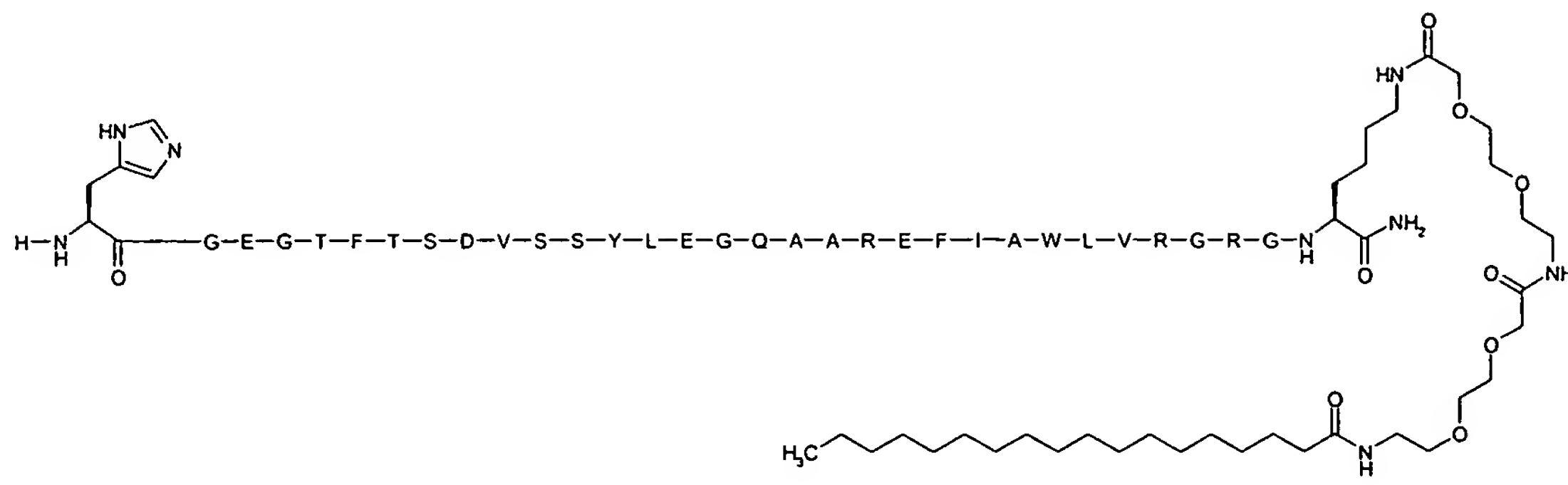


[Gly⁸, Arg^{26,34}]GLP-1(7-37)Lys((2-(2-(2-(2-(2-(2-(2-(2-(hexadecanoylamino)ethoxy)ethoxy)acetyl)ethoxy)ethoxy)acetyl)ethoxy)ethoxy)-acetyl)-OH

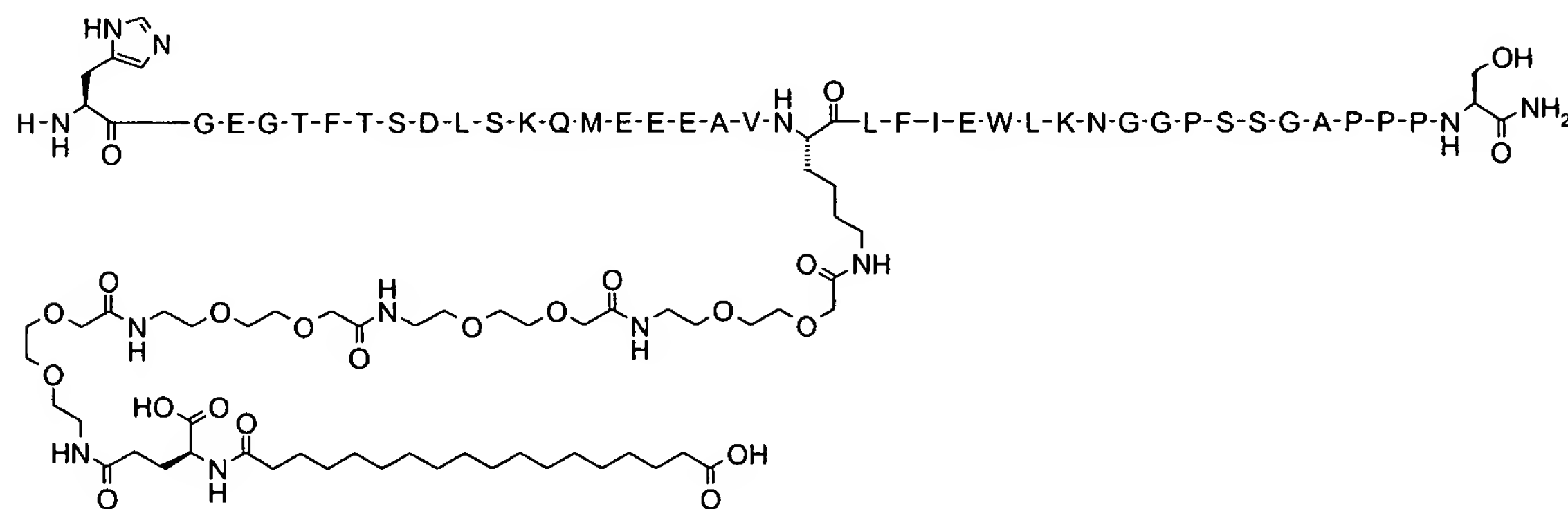


[Gly⁸, Arg^{26,34}]GLP-1 (7-37)Lys (2-(2-(2-(2-(2-(2-(octadecanoylamino)ethoxy)ethoxy)-acetyl)ethoxy)ethoxy)acetyl) NH₂

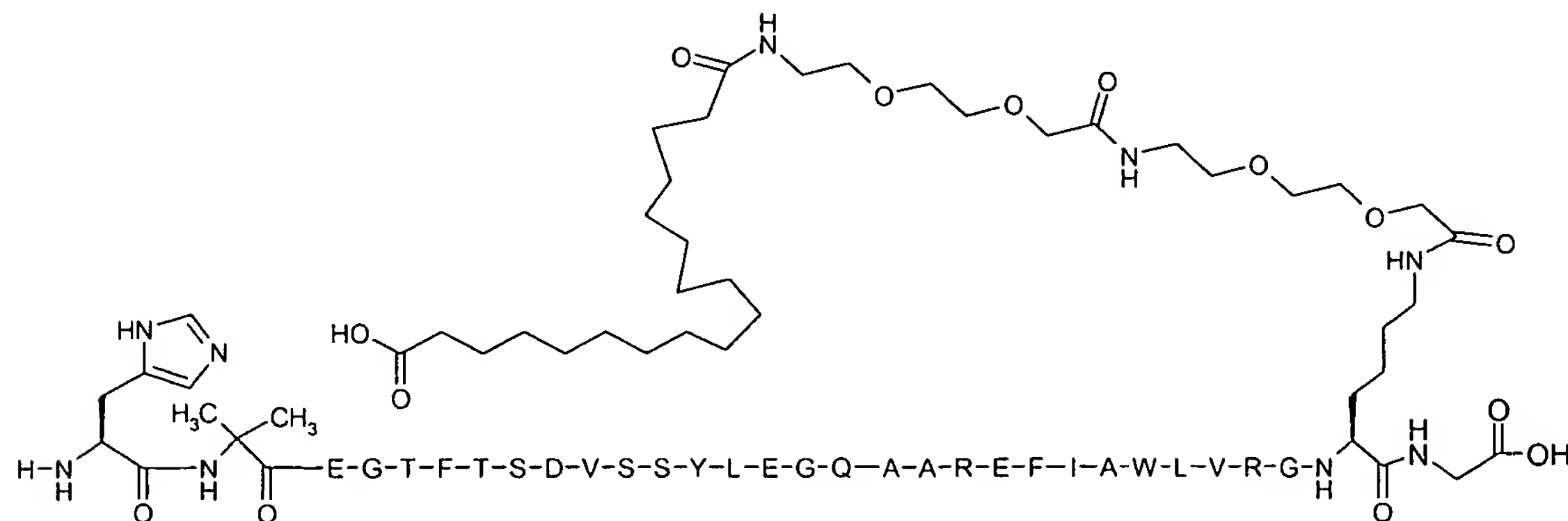
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N²⁰-(2-(2-(2-(2-(2-(2-(2-(2-(2-(2-(4-(17-(carboxy)heptadecanoylamino)-4-carboxybutyrylamino)ethoxy)ethoxy)acetylamino)ethoxy)ethoxy)acetylamino)ethoxy)ethoxy)acetylamino)ethoxy)acetyl) [Lys²⁰]exendin-4 (1-39)-NH₂

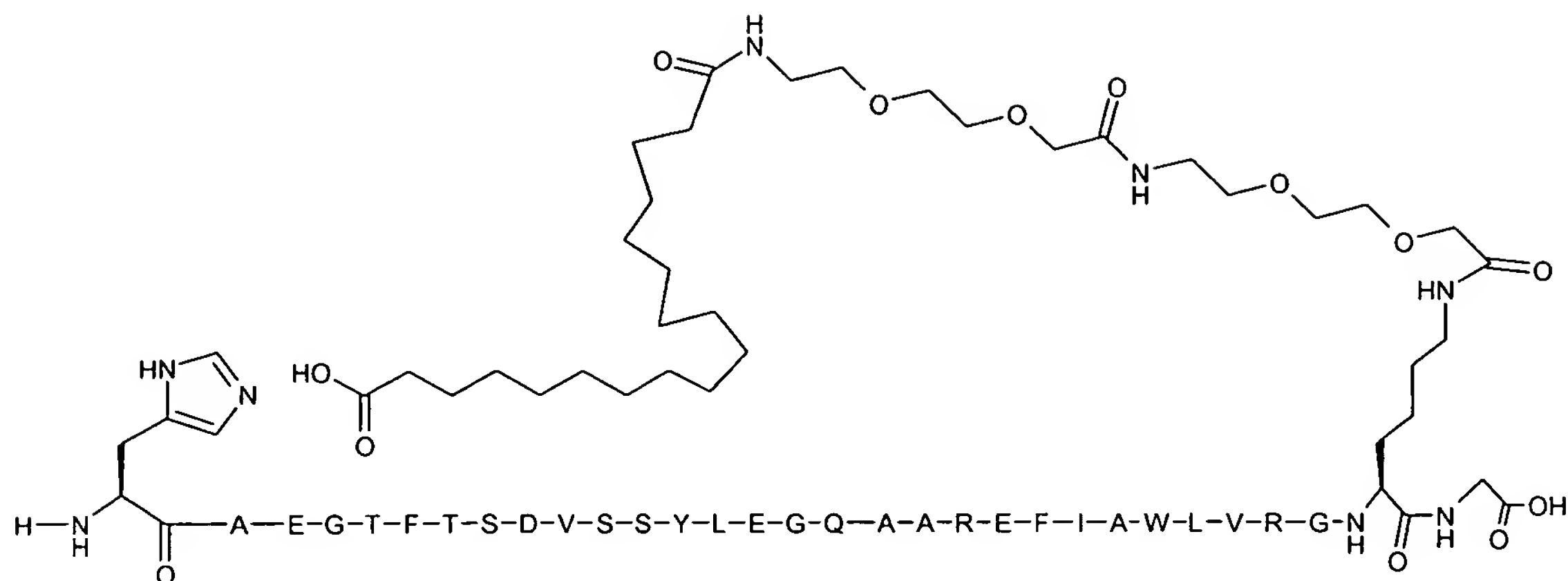
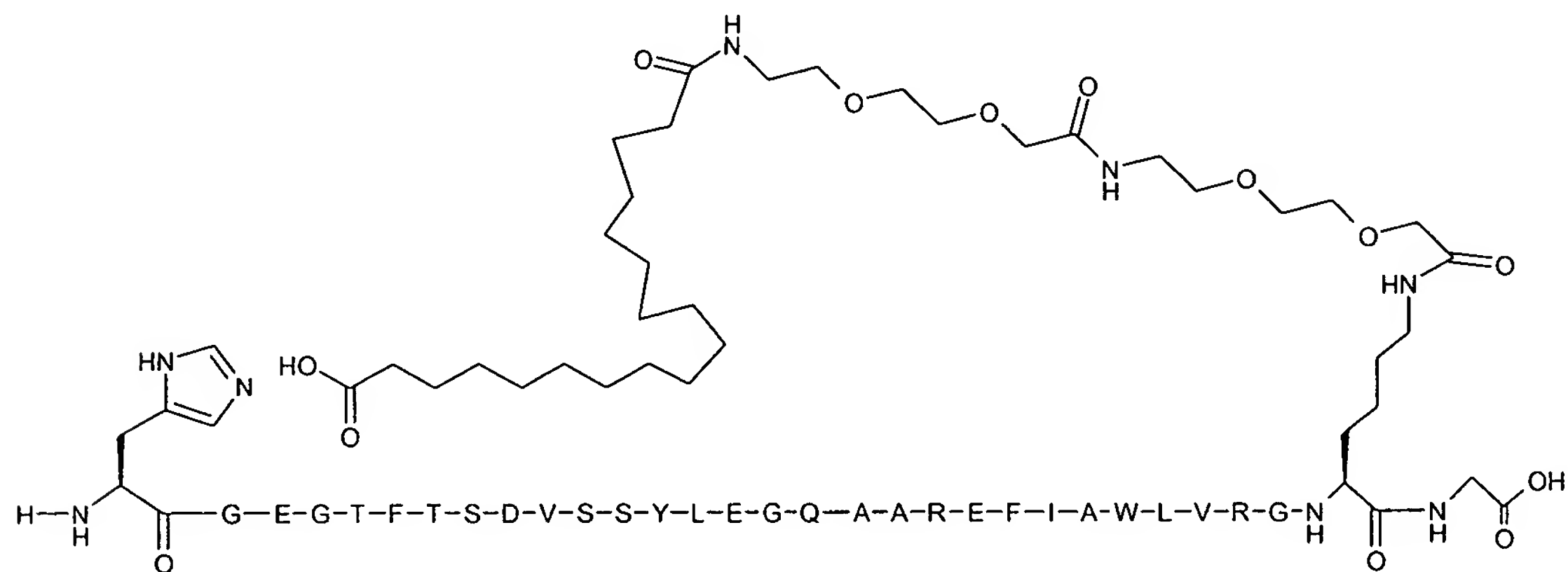


N^{ε36}-(2-(2-(2-(2-(2-(2-(17-Carboxyheptadecanoylamino)ethoxy)ethoxy)acetylamino)ethoxy)ethoxy)acetyl) [Aib⁸, Arg^{26,34}, Lys³⁶] GLP-1 (7-37)

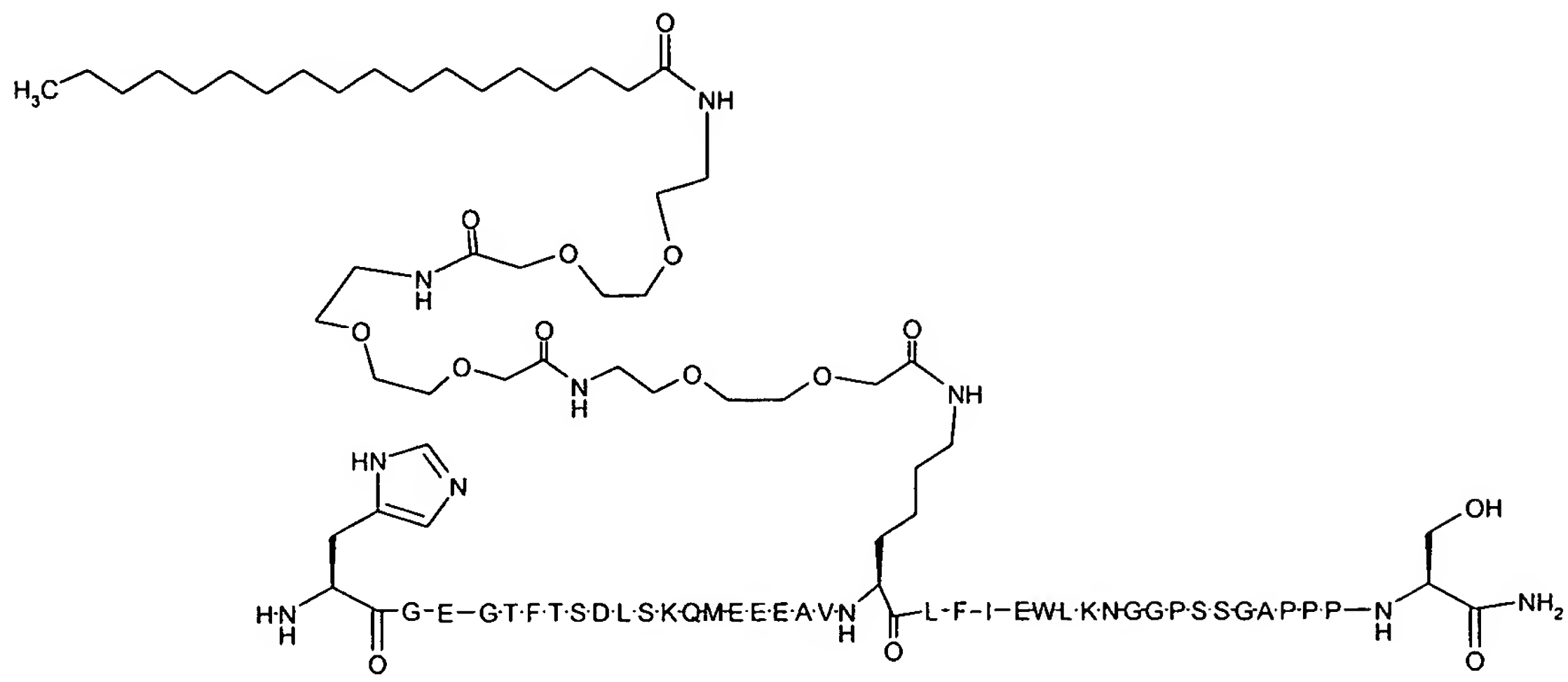


N^{ε36}-(2-(2-(2-(2-(2-(2-(17-Carboxyheptadecanoylamino)ethoxy)ethoxy)acetylamino)ethoxy)ethoxy)acetyl) [Arg^{26,34}, Lys³⁶] GLP-1 (7-37)

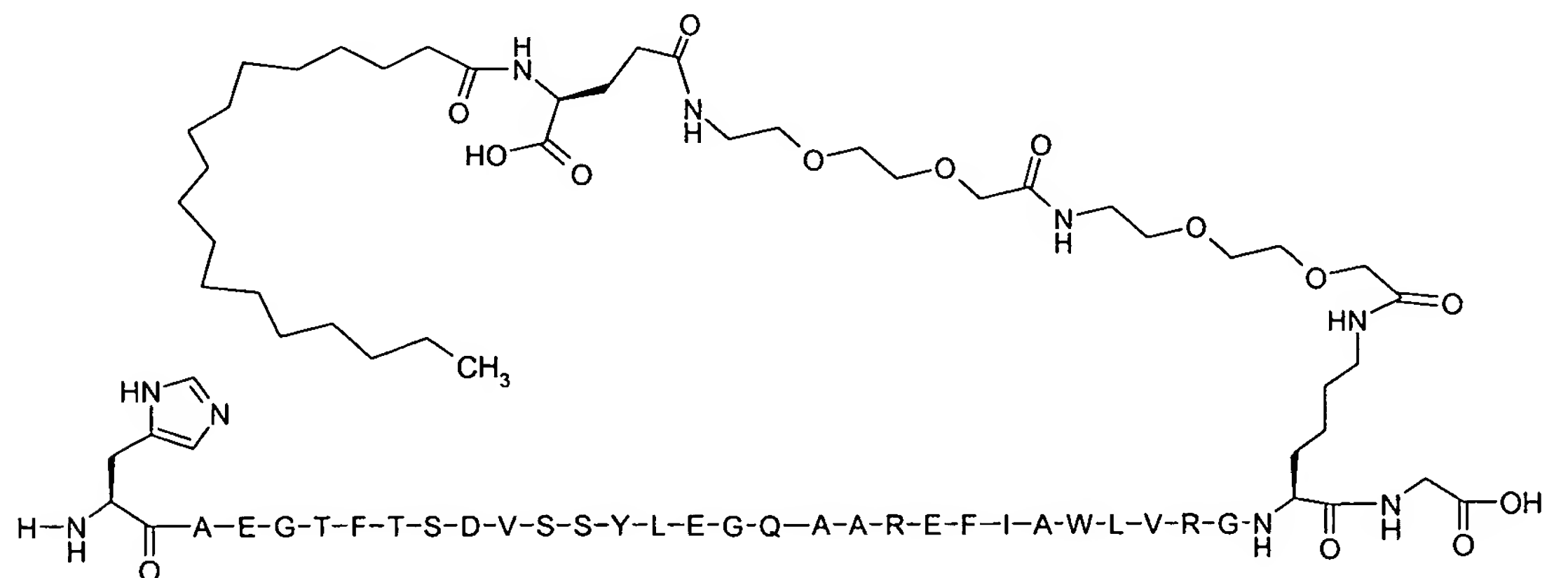
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acetylamino)ethoxy)ethoxy)acetyl) [Gly⁸,Arg^{26,34},Lys³⁶] GLP-1 (7-37)ethoxy)acetyl)[Lys²⁰] Exendin-4 (1-39)amide

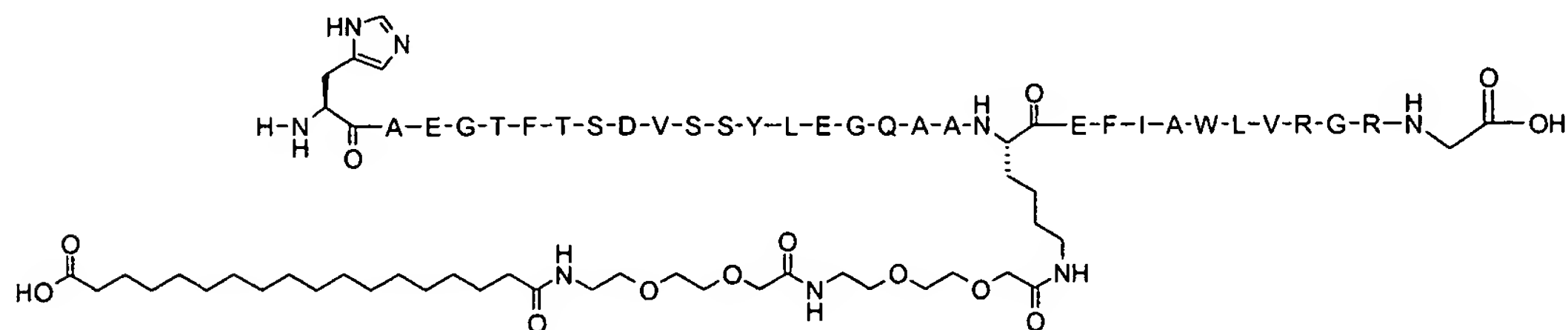
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$N^{\epsilon 36}$ -(2-(2-(2-(2-(2-(2-(4-(octadecanoylamino)-4(S)-carboxybutyrylamino)ethoxy)ethoxy)acetylamino)ethoxy)ethoxy)acetyl)-[Arg^{26,34},Lys³⁶]GLP-1-(7-37)

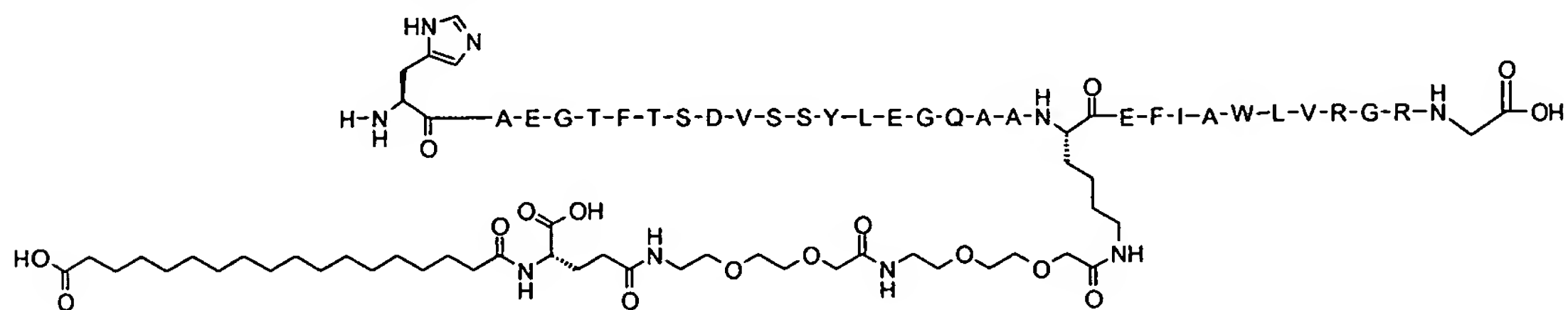


N^{222} -(2-[2-(2-[2-(2-[2-(17-Carboxyheptadecanoylamino)ethoxy]ethoxy)acetylamino]ethoxy)ethoxy]acetyl)-[Arg³⁴]GLP-1-(7-37)-OH

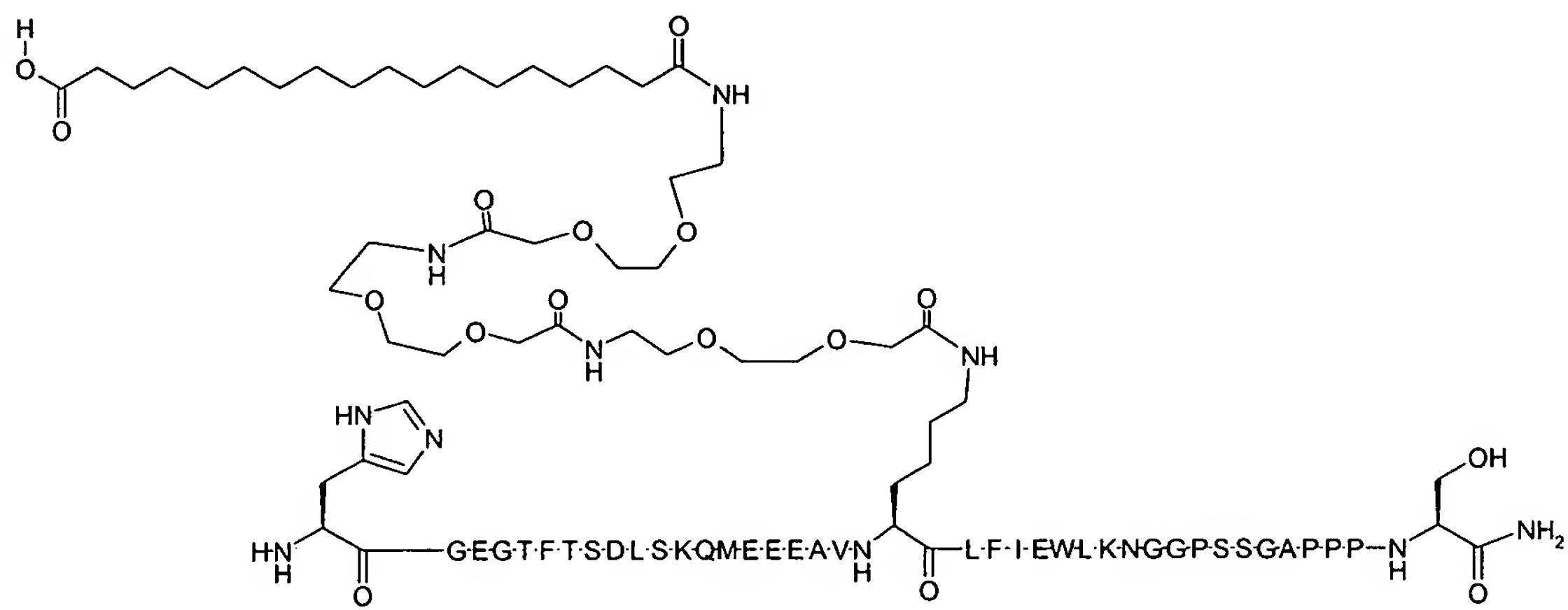


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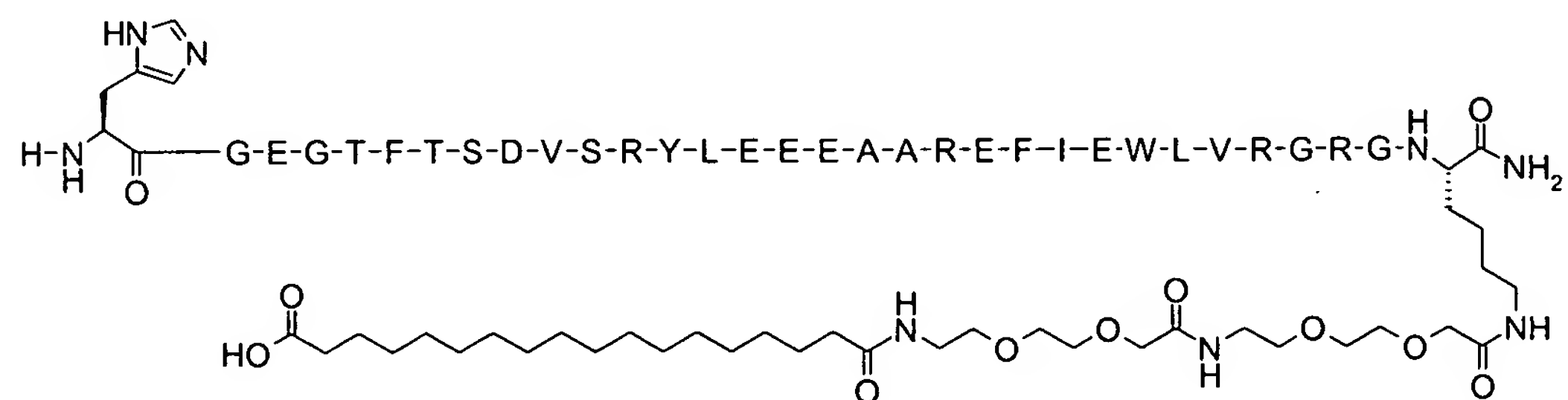
$N^{\square\square\square}$ -[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetyl)amino)ethoxy]ethoxy]acetyl][Arg³⁴]GLP-1-(7-37)-OH



$N^{\square\square}$ -(2-(2-(2-(2-(2-(2-(2-(2-(17-Carboxyheptadecanoylamino)ethoxy)ethoxy)acetyl)amino)ethoxy)ethoxy)acetyl)amino)ethoxy)ethoxy)acetyl)[Lys²⁰] Exendin-4 (1-39) amide



[Gly⁸, Glu^{22,23,30}, Arg^{18,26,34}]GLP1 (7-37) Lys(2-(2-(2-(2-(2-(2-(17-carboxyheptadecanoylamino)ethoxy)ethoxy)acetyl)amino)ethoxy))ethoxy)acetyl)-NH₂



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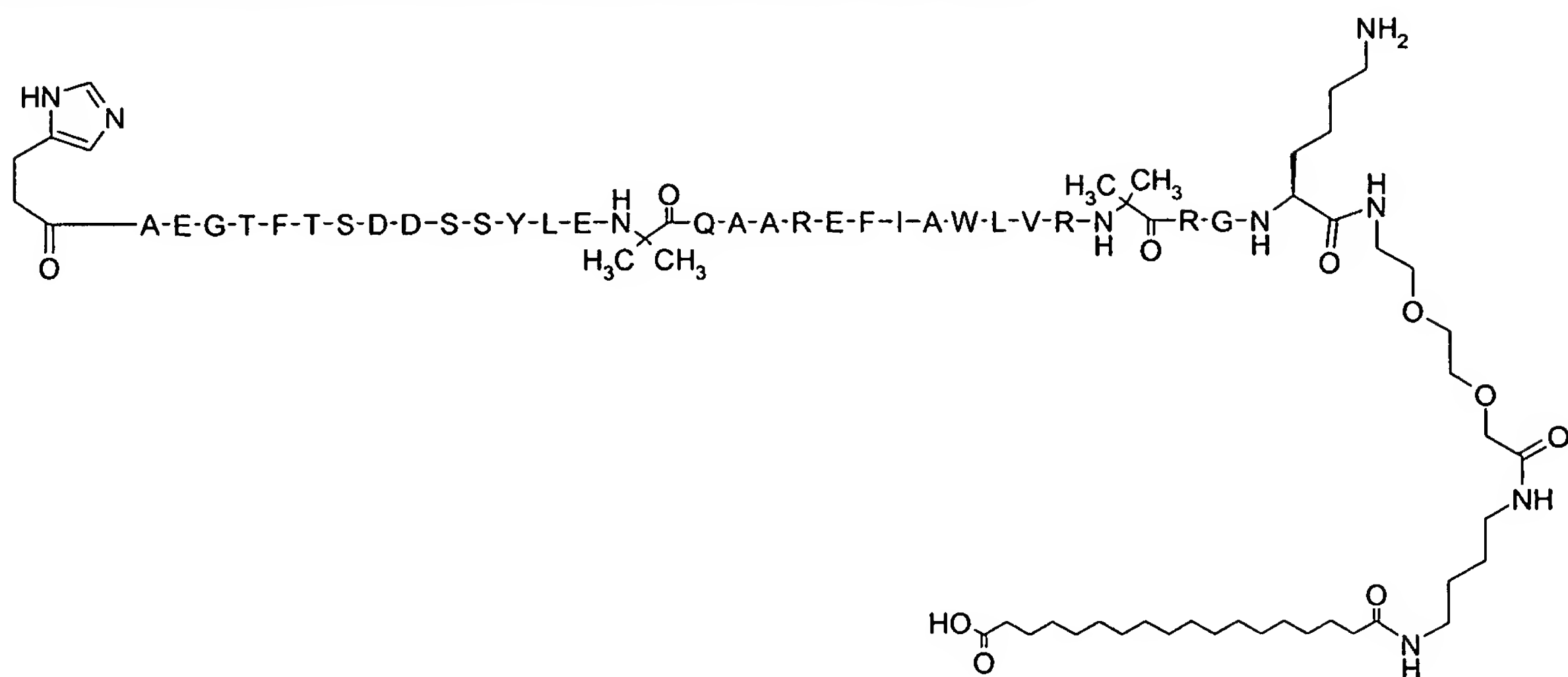
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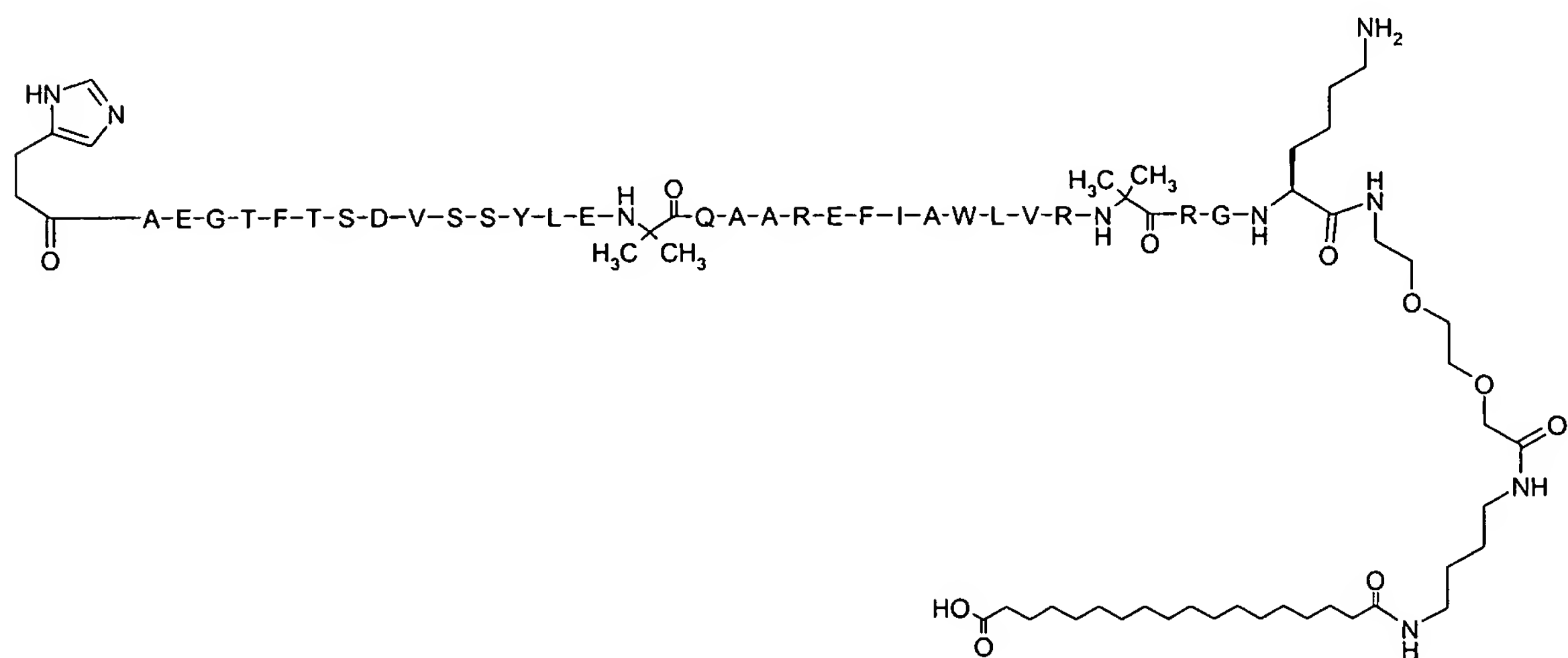
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[Imidazolylpropionic acid⁷, Asp¹⁶, Aib^{22,35}]GLP1(7-37)Lys NH((2-{[4-(17-carboxyheptadecanoylamino)butylcarbamoyl]methoxy}ethoxy)ethoxy))



,

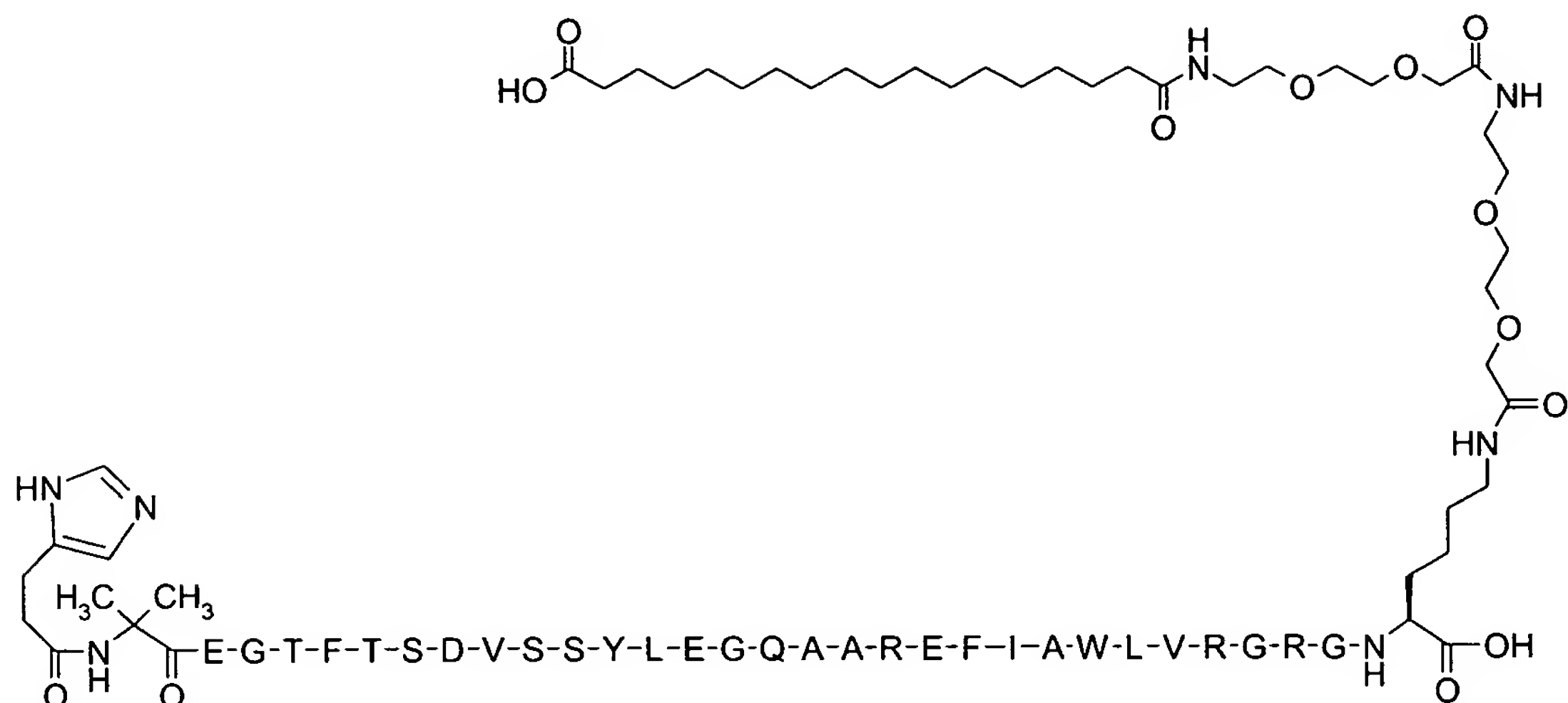
[Imidazolylpropionic acid⁷, Aib^{22,35}]GLP1(7-37)Lys NH((2-{[4-(17-carboxyheptadecanoylamino)butylcarbamoyl]methoxy}ethoxy)ethoxy))



, and

[3-(5-Imidazolyl)propionyl⁷, Aib⁸, Arg^{26,34}] GLP-1 (7-37)Lys{2-(2-(2-(2-[2-(2-(17-carboxyheptanoylamino)ethoxy)ethoxy]acetylamino)ethoxy)ethoxy)acetyl))-OH

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Claim 127 (New) A compound according to claim 73, wherein said therapeutic polypeptide is a glucagon-like peptide 2 (GLP-2) peptide.

Claim 128 (New) A compound according to claim 127, wherein said GLP-2 peptide is a DPPIV-protected GLP-2 peptide.

Claim 129 (New) A compound according to claim 127, wherein said GLP-2 peptide is Gly²-GLP-2(1-33).

Claim 130 (New) A compound according to claim 127, wherein said GLP-2 peptide is Lys¹⁷Arg³⁰-GLP-2(1-33).

Claim 131 (New) A compound according to claim 1, wherein said therapeutic polypeptide is human insulin or an analogue thereof.

Claim 132 (New) A compound according to claim 131, wherein said therapeutic polypeptide is selected from the group consisting of Asp^{B28}-human insulin, Lys^{B28},Pro^{B29}-human insulin, Lys^{B3},Glu^{B29}-human insulin, Gly^{A21},Arg^{B31},Arg^{B32}-human insulin and des(B30) human insulin.

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Claim 133 (New) A compound according to claim 73, wherein said therapeutic polypeptide is human growth hormone or an analogue thereof.

Claim 134 (New) A compound according to claim 73, wherein said therapeutic polypeptide is parathyroid hormone or an analogue thereof.

Claim 135 (New) A compound according to claims 73, wherein said therapeutic polypeptide is human follicle stimulating hormone or an analogue thereof.

Claim 136 (New) A compound according to claim 73, wherein said therapeutic polypeptide has a molar weight of less than 100 kDa.

Claim 137 (New) A compound according to claim 73, wherein said therapeutic polypeptide is selected from the group consisting of a growth factor, a somatomedin, interferon, pro-urokinase, urokinase, tissue plasminogen activator (t-PA), plasminogen activator inhibitor 1, plasminogen activator inhibitor 2, von Willebrandt factor, a cytokine, a colony stimulating factor (CFS), a stem cell factor, a tumor necrosis factor, a protease inhibitor, an opioid, a hormone, a neuropeptide, and a melanocortin.

Claim 138 (New) A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable excipient.

Claim 139 (New) The pharmaceutical composition according to claim 138, which is suited for parenteral administration.

Claim 140 (New) A method for treating hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, obesity, hypertension, syndrome X, dyslipidemia, cognitive disorders, atherosclerosis, myocardial infarction, coronary heart disease and other cardiovascular disorders, stroke, inflammatory bowel syndrome, dyspepsia or gastric ulcers, said method comprising administering to a subject in need of such treatment an effective amount of a compound according to claim 109.

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Claim 141 (New) A method for delaying or preventing disease progression in type 2 diabetes in a subject, said method comprising administering to said subject an effective amount of a compound according to claim 109.

Claim 142 (New) A method for decreasing food intake, decreasing β -cell apoptosis, increasing β -cell function and β -cell mass, and/or for restoring glucose sensitivity to β -cells in a subject, said method comprising administering to said subject an effective amount of a compound according to claim 109.

Claim 143 (New) A method for treating small bowel syndrome, inflammatory bowel syndrome or Crohns disease, said method comprising administering to a subject in need of such treatment an effective amount of a compound according to claim 127.

Claim 144 (New) A method for treating hyperglycemia, type 1 diabetes, type 2 diabetes or β -cell deficiency, said method comprising administering to a subject in need of such treatment an effective amount of a compound according to claim 131.